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SURVEY OF AIRBORNE FUNGUS SPORES OF THE BOSTON AREA IN RELATION TO INHALANT ALLERGIES

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THE ROLE of airborne fungus spores in the etiology of inhalant allergies has been firmly established by the work of many competent investigators. The first published records of allergic diseases caused by fungi were those of Cadham[4] in Canada and Storm Van Leeuwen[25] in Holland. As a result of these early reports, numerous investigators became interested in the various aspects of the problem. Reviews of the work on fungus allergy may be found in the A.A.A.S. Symposium, *Aerobiology* (1942),[1] in the excellent and comprehensive literature survey by Morrow and Lowe (1943),[14] and in *Allergy*, Urbach and Gottlieb (1946).[24]

Once clinical sensitivity to airborne fungus spores was demonstrated, an active interest in the incidence of these spores manifested itself. The first continuous record of fungus spore incidence in relation to allergy was made by Duke and Durham (1928).[5] This consisted of a two-month record of airborne rust spores in Kansas City, Missouri. Since this early work, many surveys have been carried out by individual investigators and by teams of investigators. Durham[6,7,8,9] gives data for some forty states, while Morrow, Prince and Lowe[13,15,19,20] in collaboration with The Association of Allergists for Mycological Investigations give data for various stations in eighteen states. More recently, an international survey headed by Feinberg for the Research Council of The American Academy of Allergy[12] has undertaken a program which covers forty states, Canada, and Mexico.

The importance of adequate surveys to the practicing allergist is beyond question. There has been only one limited survey of the Boston Area; and

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at the request of Dr. Francis M. Rackemann of the Massachusetts General Hospital, who felt the need for an extended survey, the present investigation was undertaken.

The study had four major objectives, as follows: (1) to determine the kinds and abundance of airborne fungus spores in the Boston area, (2) to obtain information on the fluctuation in seasonal incidence of these spores, (3) to analyze these data statistically in relation to existing weather conditions, and (4) to determine the relationship of these data to clinical sensitivity.

MATERIALS AND METHODS

In carrying out this survey considerable thought was given to the methods to be used, since the available techniques are so numerous and varied. The method finally decided upon was the plate method of aerobiological sampling because it allows for more accurate identification of fungi; yields good results on the relative incidence of different forms; allows for the isolation of those fungi which might be of further interest; and, because of the short exposure times, allows for more accurate correlation with weather conditions prevailing at the time of exposure.

The medium used was potato-dextrose agar, a complete though complex medium which permits the growth of a great variety of fungi.

The exposure sites, as originally selected by Dr. Rackemann, represented a variety of environmental conditions similar to those one might expect the average individual in Boston to encounter during the course of a day.

The exposures were made at weekly intervals for five-minute periods. This exposure time was found to be the maximum which allowed for the development of discrete colonies that did not overlap and could be easily counted and isolated after incubation.

Following exposure, the plates were sealed with adhesive tape to protect them from subsequent contamination, and the fungi were then allowed to develop at room temperature. Particular caution was observed in handling the plates throughout the period of incubation in order to minimize the danger of altering the quantitative results by seeding the plates with spores of maturing colonies.

TABULATION AND CLASSIFICATION OF FUNGI

The undisturbed plates were incubated until the colonies became discrete and could be easily counted, usually about a week, at which time the number of colonies was recorded. Lacto-phenol mounts of all macroscopically distinct colonies were examined microscopically and identified whenever possible. Colonies which did not sporulate readily or which had not reached maturity were subcultured and incubated until they could either be identified or until macroscopic and microscopic study indicated that the individual non-sporulating types did not occur frequently enough to indicate any degree of dominance and thus did not warrant further expenditure of time.

TABLE I. INCIDENCE OF AIR-BORNE FUNGI
Jan., 1948—Jan., 1949

Fungi	Percentage Incidence
Phycomycetes—Mucorales	1.1
Ascomycetes—Sphaeriales	0.6
Fungi Imperfecti Phyllostictales (Sphaeropsidales) (Not identifiable to genera, hence, lumped together as a taxonomic entity and considered as a group consisting of many genera.) Moniliales Moniliaceae Acrostalagmus Aspergillus Cephalosporium Diplosporium Gliocladium Monilia Monosporium Myrothecium Oospora Paecilomyces Penicillium Scopulariopsis Sporotrichum Trichoderma Verticillium Dematiaceae Alternaria Brachysporium Cladosporium (Hormodendrum) Coccosporium (vel. aff.) Helminthosporium Pullularia Tetracoccosporium Torula Pers. ex Fr. Stilbellaceae (Stilbaceae) Stysanus Tuberculariaceae Fusarium	75.6
Non-Sporulating and Unidentified Forms	22.7

Orders and Families of fungi after G. W. Martin.

In classifying the fungi recorded in this survey, few attempts were made to carry the identification beyond the genus. Even though there have been several reports of sensitivity to particular species,[10,17,22,23] they appear to be special cases in which the individuals were exposed to large doses of spores of the particular fungus for extended periods. Therefore, it is felt that identification to genus is usually sufficient in this type of survey.

RESULTS

Types and Abundance of Fungi.—A total of 823 macroscopically distinct colonies were recorded for the year. Most of these colonies were identifiable, and it was interesting to note that 1.7 per cent of the total belonged to the two main classes of fungi, the Phycomycetes and the Ascomycetes. There were no certainly identifiable members of the large class of the Basidiomycetes. The final proof of their taxonomic position, the presence of clamp connections, was never demonstrated. By far the highest per centage of colonies, 75.6 per cent, representing twenty-five genera and many species, belonged to the other large class of fungi, the Fungi Imperfecti.

The various fungi recorded in this survey are listed in Table I together with their percentage incidence for the year. Many of the species appeared sporadically throughout the year while certain ones, i.e., *Alternaria*,

TABLE II. INCIDENCE OF DOMINANT FUNGI

Fungi	Percentage of Total Count
Phyllostictales (Sphaeropsidales)	10.12
Moniliales	
Alternaria	18.6
Cladosporium (Hormodendrum)	11.4
Penicillium	10.6
Aspergillus	7.4
Coccosporium	3.5
Total	61.6

Cladosporium, Penicillium, Aspergillus, a form tentatively identified as *Coccosporium,* and members of the Order *Sphaeropsidales,* appeared regularly throughout the year and were invariably dominant to the other fungi.

The dominant fungi are listed in Table II in the order of their relative abundance throughout the year, and all but the form listed as *Coccosporium* were recovered during every month of the survey.

Many isolates of *Alternaria* were sent to Dr. Paul Neergaard of Copenhagen for identification because of the abundance of this genus and because of their importance as excitants of inhalant allergy. All of these cultures proved to be *Alternaria tenuis* and were used, along with other members of this genus, in clinical work to determine sensitivity to species of the genus *Alternaria.* This work will be reported at another time.

Before considering the fluctuation in incidence of the dominant forms, there are a few general points on classification and occurrence of certain species which are of interest. The classification of *Alternaria, Macrosporium, Cladosporium,* and *Hormodendrum* are of interest because of the frequency of their occurrence. Many surveys report all of these genera separately; however, present opinion considers *Alternaria* and *Macrosporium* to be identical with the former name to be given preference.[11,16,26] In like manner, *Cladosporium* and *Hormodendrum* are also considered to be synonymous with the name *Cladosporium* as the correct one.[2,3] In fact, many authorities now feel that all saprophytic species of *Cladosporium* are one species, *Cladosporium herbarum.*

The other point of interest concerns the occurrence of certain species which influence the quantitative results in sampling by the plate method. These species when they occur tend to either overrun the plate, making it difficult to isolate and identify colonies, or they inhibit the growth of other fungi. In the first category may be placed members of the Mucorales and species of *Monilia.* In the second category are members of the *Aspergillus niger* group and members of the genus *Trichoderma.* Fungi of both these groups will tend to lower the counts and hence must be given consideration if they appear consistently.

Seasonal Fluctuation in Incidence of Dominant Forms.—The fluctuation in incidence of dominant forms is shown graphically in Figure 1.

The fluctuation is shown as actual count and as percentage of the monthly totals. All the dominant forms except members of the Order Sphaeropsidales represent a high percentage of the monthly total when their incidence is high; that is, when these spores are abundant they also make up the bulk of the total number of spores for that period. Members of

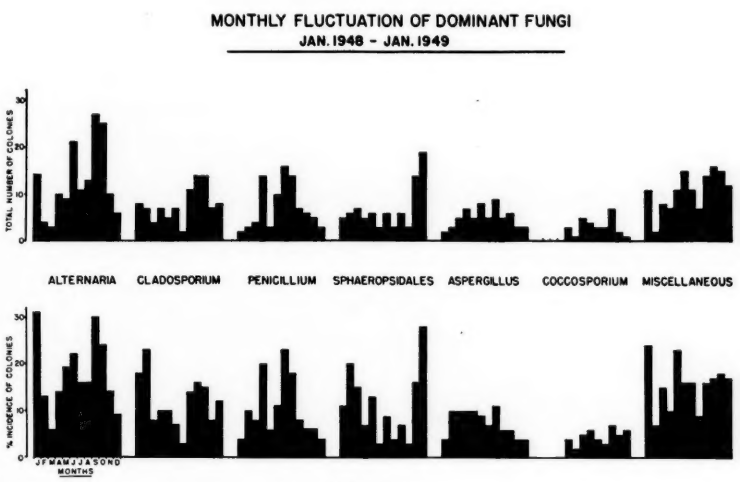

Fig. 1.

the Order Sphaeropsidales, on the other hand, remain low in actual incidence during the early part of the year but represent a high percentage of the spores present in the air during these months. In general, it may be said that all the dominant forms show some fluctuation in incidence throughout the year.

Influence of Meteorological Conditions on Spore Incidence.—It is well known that fungi require certain optimum conditions for each phase of their developmental cycle and that among the most important factors are temperature and moisture. Optimum conditions for growth may be different from those favorable for the production of spores, and for this reason it was of interest to examine these factors in relation to the total number of spores found in the air.

The factors of temperature, relative humidity, and absolute humidity were examined statistically to determine their influence on the spore count. Simple, multiple, and partial correlation analyses were carried out in order to determine the action of these factors individually and collectively.

The results of the statistical analysis showed that there was no correlation between relative humidity and spore count; whereas the absolute humidity, i.e., the actual moisture in the air, showed significant correlation.

This suggests that the term humidity should not be used loosely but should be modified to indicate relative or absolute humidity.

The analyses also indicated that during periods of rapid fluctuation of temperature, for example, during the spring and fall, the absolute humidity is important in determining the abundance of spores in the air; whereas during the summer and winter, when temperatures are likely to be fairly constant, the absolute humidity bears no relationship to the spore incidence. During these latter seasons the temperature alone is mainly responsible for observed fluctuations. Therefore, from a clinical standpoint, humid days during the spring and fall are more likely to be concerned with fungus allergies than are humid days during the summer and winter.

Upon carrying out a multiple correlation on the above data, it was possible to derive an equation from which the number of colonies or the degree of air contamination might be predicted. In order to use the equation one need only know the temperature and absolute humidity in order to make the prediction. The derived equation is as follows:

$$C(\text{count}) = 4.5 + .25\,T\ (\text{temp.}^\circ\text{F.}) - .13\,H(\text{abs. Hum})$$

An equation of this type should be of value in determing the possibility of the air being sufficiently contaminated with fungus spores on particular days to cause exacerbation of symptoms in patients who are suspected of being sensitive to fungus spores.

In addition to the weather factors discussed above, precipitation, wind direction, and wind velocity were also closely examined, but no correlation was found to exist between these factors and the fungus spore content of the air.

Relation of Survey to Clinical Cases.—As a last point, it was interesting to compare the incidence of fungus spores with the pollinating seasons in the Boston area.[21] Figure 2 shows the frequencies of the dominant fungus spores for the entire year. This is a cumulative graph; hence, the width of the individual stratum indicates the frequency of that particular fungus. Indicated by the brackets at the top of the graph are the major pollinating seasons. One can see that the major incidence of fungi occurred in the month of June and in the period from August through November and that the increase in total count during these periods was due to the increased incidence of the dominant fungi, in particular to the genus *Alternaria*. One also notices that during the fall there is a high incidence of fungus spores which persist after the end of the pollinating season. It may well be, therefore, that cases which are seasonal in character but do not respond well to pollen therapy, are complicated by fungus spore sensitivity. This may also be true of the summer cases.

In conclusion, it should be pointed out that this survey covers a period of one year only and should be carried on for a longer period in order to be more useful.

SUMMARY

A survey of airborne fungus spores of the Boston area was carried on for the year 1948 with the following results:

1. The genera *Alternaria, Cladosporium, Penicillium, Aspergillus, Coccosporium* vel. aff., and members of the Order Sphaeropsidales occurred as dominant forms.

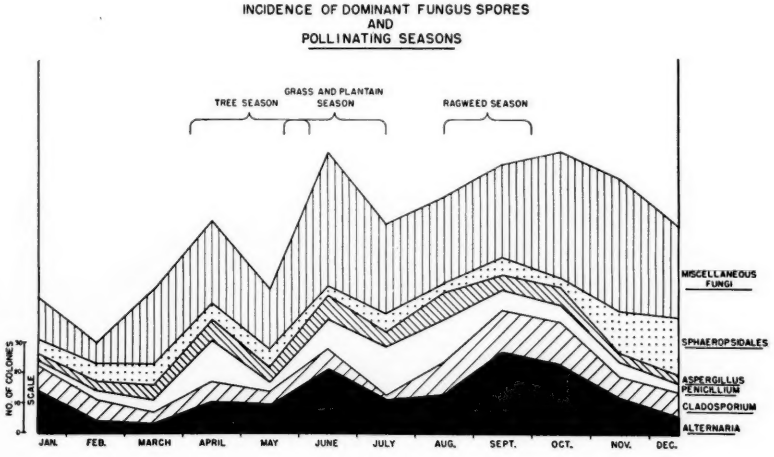

Fig. 2.

2. All of the dominant forms except *Coccosporium* vel. aff. showed a fluctuation in seasonal incidence.

3. Peak incidence of total fungus spores occurred during June and during the period from September to November.

4. Statistical analyses of the fungus spore incidence in relation to existing weather conditions showed that the absolute humidity greatly influenced the spore count during the spring and fall but not during the summer and winter.

5. An equation was derived which may be used to predict the fungus spore content of the air when the temperature and absolute humidity are known.

6. The pollinating seasons for the Boston area are compared with the fungus spore incidence for the year.

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RELIEF OF ITCHING BY OIL SOLUBLE AND SUSPENDABLE EPINEPHRINE COMPOUNDS

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THE OBJECT of this communication is first to describe experiments apparently making available for the first time comparatively stable systems of epinephrine, its isomers, and other amines for local therapy of the skin and mucous membranes dissolved and/or suspended in an oily vehicle. It will be shown that the oily vehicle may be a source of sympathomimetic activity from both dissolved and suspended epinephrine salts of certain fatty acids and salts of compounds similar to epinephrine, thus providing the slow and prolonged action so desirable in the itching dermatoses.[1,2] An apparently novel process has now been devised so that epinephrine base and similar compounds may be made to react directly with certain fatty acids in the liquid state like undecylenic acid, pelargonic acid, caprylic acid, and so on, thus transforming the insoluble epinephrine base not readily wet by oily liquids to clear solutions of the epinephrine salts. Of these acids the salts are not only polar with respect to oily liquids, but also actually soluble to a certain extent in oils like sesame oil, mineral oil, and other lipophilic liquids. In addition, by neutralizing the excess of acid by oil soluble bases the effective pH in oil can be maintained between 6 and 8, and irritant qualities due to excess of fatty acid can be reduced.

The secondary object of this communication is to show that the new procedure for solubilizing insoluble epinephrine base directly in an excess of liquid fatty acid can also be applied to other bases to form dissolved lipophilic salts of bases like histamine base, atropine base, procaine base in general, thus providing a practical new series of compounds of oil miscible and/or suspendable stabilized forms. In this way new clinical applications of basic compounds now made oil soluble and/or miscible may be anticipated.

METHOD

If a mass, e.g., one gram of epinephrine base (USP), is added to a stoichiometrical equivalent of liquid undecylenic acid at room temperature, the base does not completely dissolve. In other words, a stoichiometrical reaction between epinephrine base and the acid does not take place readily. It was important to find a solvent which would not decompose the epinephrine and which would allow the epinephrine base to react with the acid under suitable conditions to give clear solutions. It was ultimately found that undecylenic acid itself could act as the dissolving vehicle or solvent

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for epinephrine, forming a new compound, presumably epinephrine undecylenate. Thus, to achieve fairly rapid solution of one gram of epinephrine base, 27 cc of undecylenic acid is mixed with one gram of the base. This quantity of acid is much more than required if only a simple chemical reaction occurred. Usually within one hour the epinephrine base is completely dissolved. If less acid is added, the solution is much slower, and if more acid is added, the solution is more rapid.

This technique of using the acid itself as a solvent to dissolve epinephrine base is apparently a new device to dissolve epinephrine salts of the fatty acids and is not restricted to undecylenic acid. Thus, the same technique can be used with other fatty acids like caprylic acid, pelargonic acid, heptylic acid, oleic acid presumably with the formation of dissolved epinephrine caprylate, epinephrine pelargonate, epinephrine heptylate, et cetera. The solvent is the liquid fatty acid itself, maintaining the epinephrine salts in solution by the presence of secondary or other valences. Experiments were attempted with higher melting acids at high temperatures. Since the higher temperatures may result in a more rapid oxidation of the epinephrine, unless the experiments are carried out in the absence of oxygen, they are cumbersome though feasible. Although the polarity may be greater with respect to oily vehicles, experiments show that undecylenic acid, which occupies an intermediate position as far as the number of carbon atoms with a suitable melting point is concerned, takes care of the necessity of having groups, polar with respect to oily liquids, and is for the present, a type of acid of preference for obtaining both vehicle and salt formation by a single substance. There is a difference in the way in which the various fatty acids react with epinephrine base. Thus using synthetic racemic epinephrine base, 0.1 gram of epinephrine is readily dissolved in 2 cc of caprylic acid or in 1.5 cc of heptylic acid. Solution, of course, is very rapid in acids like acetic acid which, however, is not polar with respect to oily vehicles. Apparently, on the basis of these data, the shorter the length of the carbon chain the more readily is the base dissolved. However, in general, as far as our process is concerned, stoichiometrically excessive quantities are required to form the salt dissolved in the excess of the fatty acid acting as a solvent vehicle as the length of the chain increases. Mixtures of acids, e.g., of caprylic acid and undecylenic acid, also act as solvents. Experiments with petroleum ether and acetone to aid solubility did not increase the facility of dissolving the epinephrine base to any practical extent. Nor did caproic alcohol increase the solubility sufficiently to decrease the acid needed. In other words, it would appear that the action of the undecylenic acid to act as a solvent for epinephrine undecylenate is of particular value in making clear solutions of lipophilic epinephrine undecylenate. The racemic base does not dissolve as readily as the optically active material. Thus, 0.3 of a gram of epinephrine base (racemic) was added to 9 cc of un-

decylenic acid. In four days the epinephrine base had not completely dissolved.

The lipophilic nature of epinephrine salts described here may be illustrated by the following experiment: 0.3 gram of racemic epinephrine base was added to 6 cc of caprylic acid, forming a clear solution; 9 cc of sesame oil was added to this solution of epinephrine caprylate dissolved in caprylic acid. The result was again a clear solution. If much more sesame oil is added, some opalescence occurs. This solution was diluted with warm petrolatum to 150 cc. The study of the skin reactivity of this solution showed that epinephrine caprylate readily left the petrolatum mixture when applied to scratch marks in the skin and produced marked blanching on the skin. As pointed out, 6 cc of epinephrine caprylate dissolved in caprylic acid did not become cloudy with 9 cc of sesame oil. The following formula is conceivable, therefore, for a clear solution based on the foregoing ratio of epinephrine base, caprylic acid, and sesame oil. Epinephrine base: 1 mg; caprylic acid: 0.0045 cc; sesame oil: 1 cc (approximately). In this formula the caprylic acid should be neutralized by a substance like ethylenediamine or triethanolamine, and a suitable antioxidant like propyl gallate would be needed. The concentration of the propyl gallate should be at least 0.05 per cent.

As mentioned, to accelerate the solution of epinephrine base in undecylenic acid, more undecylenic acid may be used: e.g., one gram of epinephrine base dissolved rapidly in 50 cc of undecylenic acid. Each cc of undecylenic acid contained 1/50 of a gram, approximately, of epinephrine base; 0.8 of epinephrine undecylenate-undecylenic acid was diluted with 13 cc of sesame oil. This gave an approximately 1:900 system which was faintly opalescent. This solution and colloid suspension of epinephrine undecylenate in sesame oil and undecylenic acid contained a small amount of epinephrine undecylenate in suspension. This was tested for activity on the anterior aspect of the forearm by making groups of three scratches on the anterior aspect of the forearm with a binocular loupe. Definite blanching reactions were observed as high as one part in two million of epinephrine. By subsequent experiments it was shown that solutions and mixtures of this kind when filtered lose some of their activity because of their suspended but nevertheless skin reactive epinephrine. However, a good deal of the active vasoconstrictor action is left in solution. Thus, this filtered preparation showed good blanching at the end of five minutes up to 1:2,000,000 dilution; at thirty-five minutes the blanching was decreased markedly at 1:200,000 but still present in 1:20,000. At forty-five minutes the blanching was marked up to 1:2,000 and less marked at 1:20,000. Similar experiments were done with the same preparation by adding the dissolved and suspended epinephrine undecylenate to melted petrolatum. In this case blanching was observed only up to approximately 1:100,000. It would appear that the vasoconstrictor action of epinephrine undecylenate, when observed by this technique, is greater in sesame oil

than in petrolatum. After twenty-five minutes, very slight reactions were observed from 1:1,000,000, whereas this was more marked with the same material in sesame oil. After one hour the reactions were present mainly at the highest concentrations. It is of interest at this point to emphasize that the fine precipitate formed on addition of sesame oil to undecylenic acid is some form of epinephrine undecylenate. Thus, in one experiment a solution of epinephrine undecylenate that had been brought to a pH between 6 and 7 initially by cautious addition of triethanolamine was diluted with sesame oil to give a 1:1,000 dilution. The precipitate was filtered off, and the blanching area and rate of disappearance were compared on the anterior aspect of the forearm with a dense suspension of the precipitate in sesame oil. The system containing the precipitate gave blanching which lasted more than an hour and was larger in area than the filtered solution. These solutions were both stabilized by propyl gallate and there was little activity lost, if any, during filtration, since only a drop of the filtrate was required. The next day the same experiment was done with the sites reversed, with similar results. The precipitate formed on addition of sesame oil is very fine and takes a number of days to settle out. It is therefore essentially colloidal in nature. Microscopically, no definite crystal structure has as yet been observed although the precipitate in all likelihood consists chiefly of epinephrine undecylenate and norepinephrine undecylenate.

Fifteen cc of epinephrine undecylenate containing one half gram of epinephrine base and 15 cc, approximately, of undecylenic acid was diluted to 60 cc with sesame oil. No precipitate formed. This solution had been brought to approximate pH 6 (effective) previously with triethanolamine. A clear solution of oil soluble epinephrine, therefore, is feasible if the ratio of undecylenic acid to sesame oil is 1:3. An injectable clear solution of oil soluble epinephrine undecylenate should be obtainable provided that approximately 0.25 cc of undecylenic acid was present per cc of sesame oil with an epinephrine concentration being 1 gm to 120 cc and the effective pH between 6 and 7. Dilution with sesame oil may be greater with less epinephrine, but a fine precipitate forms even when less epinephrine is present. Other liquid fatty acids like undecylic acid, decenoic acid, et cetera, as well as liquid mixtures with stearic acid may be similarly used to form dissolved epinephrine salts of fatty acids.

Improved stabilization of epinephrine undecylenate has been accomplished by addition of propyl gallate, among other oxidants, to the clear solution of undecylenic acid before or after dilution with sesame oil. An excess of propyl gallate is desirable because of future dilution of the epinephrine undecylenate in the undecylenic acid-sesame oil mixture with petrolatum or other base. Thus far, uniform distribution of large quantities of propyl gallate in petrolatum has been achieved by using ethyl ether or ether-mineral oil mixtures as a solvent for the propyl gallate.

When epinephrine undecylenate-sesame oil mixtures are uniformly

dissolved and distributed in melted petrolatum, slight opalescence occurs. This opalescence is in all likelihood due to the separation of a certain amount of epinephrine undecylenate. However, the particles are small, and with solidification of the melt further appreciable aggregation does not occur. The small particle size as well as the particle size distribution in the petrolatum leads to the retention of the biological potency of this system and is of great use in the relief of itching in numerous dermatoses to be discussed.

Undecylenic acid itself applied to the skin is irritating. It has been pointed out that it is necessary to use an excess of fatty acids, e.g., undecylenic acid, pelargonic acid, and caprylic acid, et cetera, in order to obtain solution of the epinephrine. In order to diminish the irritation of the acid as far as the pH of the phase boundary of the broken skin or eczematous area is concerned, triethanolamine and ethylenediamine may be used to form the respective salts of the acids to bring the final solution to effective pH approximately between 6 and 7. The measurements of the effective pH can be accomplished as follows and give in all likelihood a representative idea of the reaction of the tissues. Indicator papers (nitrazine; hydrion papers: phenol red and bromothymol blue) of the proper pH range are moistened with distilled water. The triethanolamine, for example, is added slowly to the acid, and samples are placed on the moistened indicator paper until the suitable color is obtained. Enough of the material dissolves in water to produce fairly rapid color changes. The moistened indicator, therefore, serves as a model of the tissue and illustrates the approximate hydrolytic reaction of the epinephrine salt of the fatty acid. An example of this type of reaction is given in the following. Triethanolamine was added to undecylenic acid until pH 6, approximately, was obtained with red indicator papers. Eighty cc of undecylenic acid required 7 cc of triethanolamine. Triethanolamine undecylenate and undecylenic acid mixture of this type was essentially nonirritating to the scratched normal skin. It is of interest that 3 gm of epinephrine base and 1 gm of propyl gallate dissolved readily in this mixture. It would appear that triethanolamine undecylenate-undecylenic acid mixtures at the pH indicated readily dissolved epinephrine base in the proportion of undecylenic acid and triethanolamine indicated. The nature of the reaction, of course, will depend upon the dissociation constants of the epinephrine base and the triethanolamine, which is a stronger base. The solution of the epinephrine is, in all likelihood, also connected with the solubilizing action of the undecylenic acid mentioned in the foregoing.

Epinephrine ointments in various vehicles were tested for the presence of vasoconstrictor activity on the normal human skin by scratch technique. Thus, vanishing cream bases, benzoinated lard, as well as petrolatum, zinc ointment, ointments with liquid carbonic detergens, and similar ointments of therapeutic value were studied. The stability of epinephrine undecylenate and similar compounds in the presence of various other sub-

stances requires further elucidation. For immediate practical clinical application, however, it was found desirable to make a solution and mixture of epinephrine undecylenate, as described under "Methods," as a stock of 1:500 concentration of the base or 1:1,000 concentration of the base

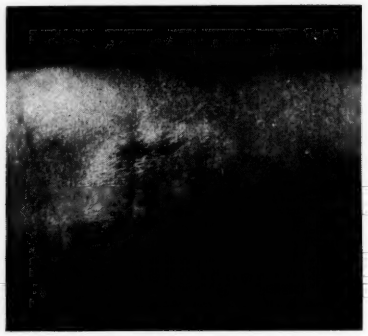

Fig. 1. Blanching due to epinephrine ointment.

and to dilute this generally to 1:5,000 with petrolatum or a modified petrolatum. The ointments preferred contain 12 per cent of sesame oil to avoid drying of the skin. With 1:3,000 to 1:5,000 epinephrine, blanching produced by the epinephrine is visible in the course of a few minutes in the scratched or opened areas of itching. Usually the relief of itching is obtained within a few minutes by the application of the epinephrine ointment. Occasionally there is slight burning at first. By combining epinephrine ointments of the types described with ointments containing local anesthetics like Nupercaine and Surfacaine, the action of the anesthetics is prolonged. A 1:500 epinephrine undecylenate ointment was applied to the face and shoulders in a severe reaction to poison ivy with relief of itching and no toxic effect.

CASE REPORTS

Case 1.—O. was a young unmarried woman, twenty-four years old, who had had a generalized neurodermatitis for several weeks. There were scratch marks on the arms, trunk and neck, with a few on the face. As therapy, 1:5,000 epinephrine undecylenate in petrolatum was smeared over more than one half of the body. Relief of the inflammation was almost instantaneous with the appearance of vasoconstriction and with relief of the itching. This ointment in this concentration was used for a period of several months with progressive improvement and relief of itching over the scratched areas. It did not relieve itching over the intact skin.

Case 2.—L. A. was a child of three years who had severe allergic dermatitis on the arms and occasionally on the legs. Incidental to an acute exacerbation, 1:5,000 epinephrine undecylenate in a petrolatum-sesame oil base was applied liberally. According to the mother and according to direct observation, the ointment produced relief of the itching and quiet sleep and aided in the healing of the lesions. This was used for a period of more than one month. (See Figure 1, which illustrates the blanching action of epinephrine undecylenate in eczema.)

Case 3.—E. S. was a twenty-three-year-old girl suffering from an allergic dermatitis of the face with marked itching about the eyes and cheeks. The patient used this ointment for fourteen days as a device to alleviate itching about the face and near the eyes, with complete healing.

Case 4.—C. R., twenty-eight years old, had asthma, eczema, and hay fever, with severe and neurogenic allergic dermatitis on the forehead and forearms occurring incidentally to emotional crises. The patient obtained immediate relief of the itching when 1:5,000 epinephrine undecylenate was applied to the forehead and the forearms except when she was under severe emotional stress; but even in this condition, itching was relieved within twenty minutes when the ointment was applied liberally. The patient used 1:5,000 epinephrine in both vanishing cream and petrolatum bases but preferred the petrolatum base. This patient has been using the ointment for relief of itching for one year.

Case 5.—R. was a fifty-year-old man with hay fever. During the hay fever season he applied a rather strong ointment (1:1,000) of epinephrine undecylenate as a thin film in the nose. Although this was slightly irritating, the patient reported that he found this a useful device to reduce itching and swelling and was able to sleep much better after applying the ointment. It was used for one month during the ragweed season of 1949.

Case 6.—B. W. was a seven-year-old boy who found that 1:3,000 epinephrine undecylenate ointment in petrolatum relieved itching about and in the nose during the ragweed season.

Case 7.—E. B. was a three-year-old boy with an allergic dermatitis and irritated, itching lesions about the nose. Epinephrine undecylenate ointment was applied locally by the mother during the ragweed season with relief of the itching. Although the 1:3,000 epinephrine undecylenate was applied successfully, the 1:5,000 was finally chosen because of diminished irritation.

Case 8.—E. L. D. was a thirty-nine-year-old man with a chronic dermatitis on his legs presumably caused by allergy, etiology unknown. There was itching which resulted in constant irritation when scratched. The 1:5,000 epinephrine ointment was applied to both legs for a period of one week, with almost immediate relief of the itching and diminishing of scratching; to quote the patient at the end of a week, "My legs are the best they have been in eight months." In the course of the next week there was an increase of the leg lesions which the ointment did not prevent. The relief of the itching, however, continued.

Case 9.—T. was a veterinarian with a severe allergic dermatitis of both hands and the left wrist. Itching was relieved by the 1:5,000 ointment, but there was irritation with this concentration. Dilution to 1:10,000 epinephrine proved more serviceable in relieving itching without irritation.

Case 10.—C. was an unmarried woman of twenty-seven years who had untreated hay fever. The 1:1,000 epinephrine undecylenate ointment smeared liberally on the swollen turbinates produced fair relief of the swelling, but a moderately severe sneezing episode on several occasions resulted.

Case 11.—T., a thirty-year-old man who had been working in the woods, had a severe attack of what was apparently poison oak poisoning with extremely severe lesions on the face, shoulders, arms, legs, and genitals. As therapy, 1:500 epinephrine

undecylenate ointment was liberally applied, with relief of itching. At the same time 0.2 cc of 1:1,000 epinephrine solution was injected. It is of interest that only mild constitutional reaction to epinephrine was observed following combined therapy with ointment and parenteral therapy.

Case 12.—H. A. A., the writer,[3] applied 1:500 epinephrine ointment to himself in an extensive case of poison oak poisoning involving the face, neck, shoulders, and back. There was relief of the itching for several hours after the ointment was applied, and no constitutional symptoms whatsoever were observed.

Case 13.—W. was a photographer who had had a severe dermatitis of both hands. There was a secondary infection of the palms with numerous pustules. As therapy, 1:500 epinephrine undecylenate was liberally applied. There was immediate relief of itching and congestion, with rapid healing within a week during the time the ointment was liberally applied several times daily.

TABLE I. DATA OF DR. L. SCHWEICH

Diagnosis	No. Cases	Results	Side Effects
Atopic dermatitis	6	good	irritation in two cases (erythema)
Contact dermatitis	2	fair	1: no side effect. 2: aggravated
Pruritus ani	3	good	none
Pruritus vulvae	2	good	1: ("burning") no visible symptoms.
Pruritus (generalized)	1	poor	none
Ichthyosis	1	none	none
Urticaria	2	none	none
Neurotic excoriations	1	none	none
Total	18		

Dr. Leo Schweich, of New York City, studied the epinephrine undecylenate ointment and was kind enough to submit the following report on March 22, 1950.

"The following is a short report on my experience in the treatment of different skin conditions with the epinephrine undecylenate ointment which you put at my disposal some time ago.

1. The total number of patients treated was eighteen.

2. The diagnoses included pruritus ani, pruritus vulvae, generalized pruritus, ichthyosis, urticaria, atopic dermatitis, contact dermatitis, and neurotic excoriations.

3. Of the various bases used (Neo Base, lanolin, aquaphor, and vaseline), I had the impression that petrolatum was most suitable for the following two reasons: namely, the applications of the ointment in a petrolatum base appeared to be more efficacious and at the same time less irritating.

4. The various strengths used in the beginning, such as 1:1,000 and even higher concentrations, have been irritating in most cases. The concentration used lately, namely, 1:1,500, appeared to me the "optimum percentage."

5. My results in the treatment of neurotic excoriations, ichthyosis, urticaria and plain pruritus genitalis (by this I mean a pruritus without any visible cutaneous changes) have not been very convincing.

6. Results in atopic dermatitis in general and in some of the cases with contact dermatitis were much more encouraging.

7. These facts apparently show that the preparation does not work in cases where the epidermis is intact, while the better results in cases with atopic dermatitis, genital pruritus, et cetera, could be explained by the fact that in these cases the

epidermis was not intact and the epinephrine could exert its action because of the presence of primary skin lesions or scratch effects.

8. In the latter group, which otherwise responded favorably, a small number of patients complained of "burning," and the treatment had to be discontinued temporarily because of "irritation."

DISCUSSION

It is of interest to illustrate how undecylenic acid may be used as a solvent for other salts of undecylenic acid. One gram of histamine base was dissolved in 20 cc of undecylenic acid and diluted to 100 cc with sesame oil. A clear solution was obtained. The activity of this solution on scratching the skin and moistening the scratches with the oily solution of histamine undecylenate was observable at a 1:1,000,000 dilution. It may be mentioned that it is desirable to bring the solution to an effective pH of about 7.0 before using it on the skin. By using the oily solution of histamine undecylenate, the antihistaminic effect of epinephrine undecylenate in oil may be simultanously studied. One to five hundred of epinephrine undecylenate inhibits completely 1:1,000 histamine undecylenate in oil, but does not markedly affect under our conditions 1:100 histamine undecylenate. The restoration reaction (Abramson and Grosberg) of epinephrine was observed, however, after a wheal was produced. Thus after fifteen minutes a wheal about a scratch produced by 1:300 histamine undecylenate, treated initially with 1:500 epinephrine undecylenate, disappeared; and in place of the wheal the white area produced by epinephrine was observed. This is the same phenomenon of restoration of the epinephrine blanching observed previously by the electrophoresis of histamine into an area treated with epinephrine. This histamine undecylenate is not completely in solution. In the 1:100 system there is a slight haze which decreases with dilution with sesame oil.

By chance the effect of histamine undecylenate in oil on healing of the skin was observed. The scratch marks treated with histamine alone healed more quickly on the anterior aspect of the forearm than those scratch marks which had been treated by both epinephrine and histamine and by sesame oil alone. It may appear that in this system histamine undecylenate stimulates healing because of the effect on the minute vessels of the skin and the lymphatic supply. It would be of interest to study the effect of dilute histamine undecylenate in oil on wound healing under more controlled conditions.

Histamine undecylenate deteriorates even though it is in oil in the presence of oxygen. Some stabilizing agent like propyl gallate is needed, or the material should be stored in the absence of oxygen.

A 2 per cent solution of ephedrine undecylenate in sesame oil may be readily prepared by adding one half gram of ephedrine base to 4 cc of undecylenic acid, and diluting with 21 cc of sesame oil.

Atropine base is not readily soluble in sesame oil, but 0.1 gram atropine base plus 2 cc of undecylenic acid may be diluted with 10 cc of sesame oil

to form a clear solution. A suitable medically useful solution can be made by dissolving 0.1 gm of atropine in ½ cc of sesame oil and diluting with 100 cc of sesame oil.

Caffeine is soluble in an excess of undecylenic acid; it may be diluted with sesame oil to form soluble caffeine undecylenate.

The foregoing data illustrate in general the types of compositions which may be made with a certain base using aliphatic acids like undecylenic acid as a solvent. Thus is made available slow acting salts of histamine, atropine, and epinephrine by the use of the solubilizing action of undecylenic acid and similar aliphatic acids, the salts being initially soluble in an excess of fatty acid and forming to a certain extent oil soluble salts in sesame oil, peanut oil, olive oil, soya bean oil, and similar oils in use in medicine. In the case of admixture with petrolatum the lipophilic nature of the mixture renders these salts pharmacologically desirable and biologically active. Of particular interest is the atropine undecylenate system. It might be of use in the therapy of gastric ulcer and similar conditions where a prolonged parasympathetic block is desired.

SUMMARY

1. Procedures are described for the preparation of comparatively stable systems of lipophilic epinephrine salts dissolved and/or suspended in oily vehicles. These procedures are embodied in the principle of using an excess of a liquid fatty acid as a solvent for its own salt of insoluble epinephrine base.

2. The oily vehicle or essentially water-free ointment may be a source of sympathomimetic activity to provide slow and prolonged action of epinephrine.

3. Oil soluble and/or miscible compounds of epinephrine with undecylenci acid, pelargonic acid, caprylic acid, and other acids are described. Thus insoluble epinephrine base is readily wet by oily liquids to form clear solutions of epinephrine salts.

4. The procedure for stabilizing insoluble epinephrine base can also be applied to other bases to form lipophilic salts of histamine, atropine, and procaine.

5. The antihistaminic and antipruritic action of epinephrine undecylenate was observed with very high dilution and is practically applicable in concentrations as high as 1:500.

6. 1:5,000 epinephrine undecylenate ointment is the concentration of choice.

7. The ointment was used for periods of months in the same patients with no untoward effects.

8. Case reports are given in which epinephrine undecylenate ointment was used in atopic dermatitis, contact dermatitis, pruritus ani, pruritus vulvae, ichthyosis, urticaria, poison ivy, and neurotic excoriations.

9. Epinephrine undecylenate ointment relieves itching in all cases where there are either minor or major breaks in the continuity of the

skin. Therefore, favorable results were obtained in neurodermatitis, atopic dermatitis, poison ivy, contact dermatitis, pruritus vulvae, and pruritus ani.

10. An isolated observation on the effect of histamine undecylenate in oil on accelerated healing of the skin is reported.

NOTES

1. It is of interest that a 1:2,000 epinephrine solution in water was previously used as a decongestant for weeping eczema.—The Pharmacopeia and the Physician. Page 127. Chicago: AMA, 1940.

℞ Solution of epinephrine hydrochloride.....15.00 cc
Wool fat ..... 5.00 Gm
White petrolatum .....10.00 Gm
Mix and label: Apply to the affected skin. (Presumably 1:1,000 epinephrine solution—H.A.A.)

2. For the usual ways of making epinephrine ointments, see U. S. Pharmacopeia and National Formulary.

3. Present clinical studies are with *epinephrine base itself with the particles ground to 15μ and below.* This ointment of the base is less irritating and has been safely applied to large scratched or eczematous areas of the body with no constitutional effects but with symptomatic relief of itching.

4. An important modification of the stabilization of the particles consists in coating the individual particles with propyl gallate. After the individual epinephrine particles are coated with propyl gallate, the larger clusters of particles are mechanically disintegrated anaërobically by a vibrating disintegrator. These particles suspended in mineral oil are again homogenized anaërobically and the fine suspension of particles ($< 10\mu$) of epinephrine base coated with propyl gallate is uniformly distributed in petrolatum. This petrolatum ointment may be mixed with other types of ointments. Concentrations from 1-500 to 1-5000 of epinephrine base produce blanching consistently on areas of the skin which are broken and relieve pruritus as indicated in the foregoing.

At no time have hypertensive effects been observed, even though large areas of the body have been treated. The ointment, as now prepared, is especially useful in the allergic type of contact dermatitis similar to poison ivy.

The same process can be applied to the organic salts mentioned in the foregoing paper as well as to inorganic salts of epinephrine.

By coating the epinephrine base and salts with propyl gallate, a remarkable increase of stability in our preparation has been observed. Thus, epinephrine ointments kept at 50° C. for one month show little, if any, change in color or diminution in vasoconstrictor activity on the scratched human skin. A slight brownish tint is observed after two months at 50° C. Because of this high degree of temperature stability, our ointments are now kept at room temperature for routine use.

133 East 58th Street

PROLONGED EPINEPHRINE ACTION

A Report on Use of An Epinephrine Suspension

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EPINEPHRINE has been the backbone of therapy in several allergic diseases since it was isolated by Takamine in 1901. Its greatest usefulness has been in treatment of bronchial asthma, urticaria, and drug reactions. It is still the treatment of choice for asthmatic attacks in children.

One of the greatest objections to the use of epinephrine has been the relatively short duration of beneficial effects. Because of this, the severely ill patient tends to take repeated injections (or inhalations) of it; this sometimes leads to adrenaline-fastness. Any device by which the action could be prolonged would result in a lower incidence of this condition.

Until recently, there has been only one generally accepted method of prolonging the action of epinephrine. This has been by the use of intramuscular injections of epinephrine in oil. The preparation which we have used for many years is a 1:500 suspension of epinephrine in peanut oil. To the best of our knowledge, we have seen only two reactions to it which could be attributed to the oil itself (both in peanut-sensitive patients).

There have been several objections to the use of this product. Prime among these has been the variation in time of onset and duration and intensity of epinephrine effect. In general, the patient will develop mild jitteriness (and relief of asthma) in about thirty minutes, with therapeutic effects lasting four to eight hours (sometimes a bit longer). However, some patients will develop marked side effects within a short period of time.

Another objection has been the mode of administration: many patients find gluteal injections objectionable on esthetic grounds. Children start screaming at the sight of the long needle necessary for this type of injection. A number of patients note that some of the oil leaks out after the injection, staining the clothes.

None of these objections is sufficient to cause us to abandon this type of treatment. We believe that most asthmatic patients are benefited by epinephrine in oil. We have used literally tens of thousands of ampules in past years. Most of these injections have been given in conjunction with either intravenous aminophylline or subcutaneous aqueous epinephrine.

Recently, a new product has been brought to our attention as a substitute

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for epinephrine in oil. This product is a 1:200 suspension of epinephrine in a base of 10 per cent glycerine, 2 per cent sodium thioglycolate, and 0.5 per cent chlorobutanol. The solution is called Sus-Phrine.®*

The main advantage of this product is its mode of administration. Instead of gluteal injections with a long needle, Sus-Phrine is given subcutaneously with any ordinary tuberculin syringe and fine short needle. We ordinarily use a ½-inch 27-gauge needle and have never had a needle stop up during an injection of Sus-Phrine (an estimated 1,000 injections by patients or by us).

We have now used Sus-Phrine in 173 patients and are adding new ones daily. As with epinephrine in oil, most of these have been given in conjunction with other types of antiasthmatic therapy. In these instances, it is difficult for the patient to evaluate the exact efficacy of the new product. However, all but three have stated emphatically that they prefer the new product to epinephrine in oil; they agree that the two injections produce similar therapeutic effects. Except for the aforementioned three, those who had any preference preferred Sus-Phrine.

Greatest individual acceptance of the new injection has been by children. No longer need they be frightened by intramuscular injections. Instead, we usually give the Sus-Phrine right with the ordinary desensitization injections, using similar needles and syringes. Average dosage in children is only 0.20 cc (in adults 0.40 cc). All injections of this substance are given deep subcutaneously in the upper arm. There is no pain immediately with the injection; within about thirty seconds most patients complain of mild to moderate stinging in the area of the injection. This is not enough to make the average child cry and persists only a few minutes.

The only other local ill effect observed in this group of 173 patients has been transient development in three patients of a red, tender, swollen area up to the size of a walnut. None of these reactions was accompanied by fever, lymphadenopathy, or malaise. All three patients have had subsequent injections of Sus-Phrine with no ill effects. (Two of these patients are among the three mentioned above who prefer epinephrine in oil.)

The only generalized ill effects reported by patients (and these are unusual) are those due to epinephrine—jitteriness, palpitation, and occasional nausea. The patients who cannot take epinephrine usually have marked side effects from Sus-Phrine. One of the patients who likes the new product best is a man who has always had very marked ill effects from aqueous epinephrine or epinephrine in oil. Half doses of Sus-Phrine have proven definitely beneficial to him.

Therapeutic effects usually become evident in about twenty minutes, although they may appear as soon as ten minutes after injection. The relief lasts an average of six to ten hours—frequently longer. Most

*Manufactured by Brewer & Company, Inc., Worcester, Massachusetts.

patients who have compared the two products state that benefits from Sus-Phrine persist longer than those from epinephrine in oil.

In addition to its use in the office or on house calls by the physician, Sus-Phrine is well suited for use by the patient himself. Any patient who gives himself epinephrine by injection can just as easily inject Sus-Phrine. In fact, the new product is better for home use because of the prolonged duration of relief, which necessitates fewer injections. The dosage is small enough to be handled easily (0.30 to 0.40 cc in adults; 0.15 to 0.20 cc in children).

Sus-Phrine is available in sterile 5 cc multiple dose vials, which need not be refrigerated. The vials should be kept in a box and not exposed to light; before injection, the solution must be thoroughly shaken. Frequently, the last few drops in the vial become discolored and appear cloudy and yellow-brown. Tests by the manufacturer have disclosed no changes in potency at these times.

SUMMARY

1. Prolonged epinephrine effects for treatment of bronchial asthma and urticaria can be obtained through the use of a suspension of epinephrine in a glycerine base; this product is known as Sus-Phrine.

2. This product has the advantage over epinephrine of prolonged therapeutic effect, necessitating fewer injections. There is less chance of a patient becoming epinephrine-fast through its use.

3. Advantages over epinephrine in oil are ease of administration, relative painlessness, and diminished expense to both patient and physician. Experience in 173 patients showed that Sus-Phrine was preferred by all but three. These patients stated that Sus-Phrine gives as good as or better relief than epinephrine in oil, with longer duration of action. It may also be useful in some patients who cannot tolerate aqueous epinephrine.

4. Sus-Phrine is particularly adaptable to use by the patient in the home. Average dose is 0.40 cc for adults, 0.20 cc for children.

Acknowledgment: The authors are indebted to Dr. Paul C. Barton and Brewer & Company, Inc., for the material used in the study.

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METHODS OF IMMUNIZATION EMPLOYED IN THE TREATMENT OF SINUSITIS

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WITH the methods at our disposal today, the solution of the problem of the management of sinusitis is a comparatively simple matter. Before the introduction of allergic methods of treatment and the use of antibiotics, surgical interference offered the only approach to the problem.

DIAGNOSIS

In the present management of sinusitis, however, satisfactory results are dependent upon accurate diagnosis, for there is a definite relationship between the condition under consideration and the method to be employed in treatment.

The inflammatory diseases of the paranasal sinuses may be divided into three groups as follows:

1. Infections
   (a) Acute, subacute and chronic
2. Allergy
3. Allergy with infection
   (a) Acute, subacute and chronic

Before any method of treatment is instituted, it is necessary to determine which of these conditions is present. In dealing with the pure infections, an acute or subacute exacerbation of a chronic sinusitis may be difficult to recognize. In the management of allergic sinus disease, acute and subacute infections commonly complicate the picture, and superimposed chronic infection must be carefully evaluated. Dental infection of antrum may complicate a pure allergy in other sinuses.

Accurate diagnosis is dependent upon the correlation of the following:

1. Clinical history
2. Local examination
3. Cytology of the secretions
4. Bacteriology (pyogenic, virus or fungus organisms)
5. X-ray examination
6. Pathologic examination of tissues

In this chain of six diagnostic links, the cytology of the secretions is the most important single guide in diagnosis. The number of neutrophil or eosinophil cells and their proportion are of definite significance. If the process is one of infection, as indicated by the presence of neutrophils, the type of pyogenic virus or fungus organisms should be determined. The extent of gross pathologic changes may be determined by the local and

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x-ray examinations. Finally, the clinical history is correlated with all other factors.

TREATMENT

In the management of sinusitis, the following methods may be employed:

1. Local and surgical
2. Antibiotic
3. Allergic
   (a) Immunization—infection and/or allergy
   (b) Hormones—ACTH and cortisone, thyroid endocrine substances

With this diversity of methods of treatment, it is evident that the primary diagnosis is important. The principles of treatment of the nose and paranasal sinuses presented here are also applicable to the lower respiratory tract. In purely allergic conditions, surgical interference or the use of antibiotics is primarily not indicated. In infections, especially those which complicate allergy, ACTH or cortisone should not be administered.

IMMUNOLOGIC (DESENSITIZATION) THERAPY IN INFECTIONS AND IN ALLERGY

The methods which have been employed in the past, based upon immunization or desensitization by means of vaccines, have not been satisfactory so have been almost entirely discarded. In the management of all acute, subacute, and even chronic infections of the paranasal sinuses, the use of the antibiotics plays an important part. Although we appreciate their value in the control of infections, there is great need for the development of methods of immunization which will prevent or greatly attenuate the establishment of acute infections such as the common cold (caused by virus organisms) and the pyogenic processes caused by Staphylococci, Streptococci, Pneumococci, influenza, and other related organisms. An ounce of prevention is still worth a pound of cure.

The administration of large doses of antibiotics, especially when prolonged, may lead to a disturbance of the biotropic balance, as the result of which fungus infections such as, for example, moniliasis of the mouth, lungs and intestinal tract, may occur. Biotropic balance is also disturbed by the use of ACTH and cortisone in that the resistance to infection may be lowered to a serious degree, as recently reported in cases of pulmonary tuberculosis.

The serum sickness-like reactions, such as those manifested by urticaria and angioedema, for example, are commonly encountered today, especially from the use of penicillin. The administration of penicillin and other antibiotics in the treatment of minor infections and the common cold

should be discouraged. Some of the serum sickness reactions constitute a greater illness than the original infection.

The antibiotics are much overused in children: they are being administered for all types of minor infections. Although allergic reactions to them are not as common as in adults, the effect of the disturbance of the biotropic balance or the possible interference with the development of the state of natural immunity to the organisms commonly encountered in the respiratory tract remains to be determined. We have recently adopted the plan of giving smaller doses or increasing the intervals between them with the idea of attenuating the infection rather than trying to eradicate it. In this manner, a certain degree of natural immune reaction to the infection is permitted to occur.

VACCINES AND TOXOIDS

For many years we have employed mixed respiratory vaccines for the prevention or treatment of common colds. The original material was serially diluted to 1:10, 1:100, et cetera, up to 1:1,000,000. We felt that some results were obtained with dilutions of 1:1,000 and 1:10,000, but they were of course difficult to evaluate. An attempt was made to find an optimum effective dosage. The idea of progressively increasing the dosage was not followed because such a plan of immunization had been previously discarded as useless.

More recently we have discovered that Staphylococcus toxoid when injected intracutaneously in doses within the range of 1/10 unit to 1 unit (usually 1/2 unit) will produce a remarkable immune response in cases of furunculosis of the external auditory canal. This effect had never been observed in using the standard plan of beginning with a dose of 10 units and gradually increasing it to 1,000 units per dose. The small optimum doses were found to be effective for about three to four days.

The effect of acute infections, fever, trauma, operations, burns, fractures, et cetera, on allergy has been known for a long time, in that such conditions as asthma or urticaria may quickly disappear with their introduction. This effect is considered as nonspecific. We found that this response could be obtained by the injection of the optimum doses of Staphylococcus toxoid referred to above. In post-penicillin urticaria quick relief may be obtained with a dosage of 1 unit. In infantile eczema, good results have been noted with doses of 1/10 to 1/2 unit.

These observations on the effect of small so-called optimum doses originally began in 1935 with the use of the principle in the treatment of pollen and dust allergies. So far, vaccines and toxoid have also been used in the treatment of arthritis with some satisfactory results.

Now we are interested in the treatment of the common cold and acute pyogenic infections as they involve the nose and paranasal sinuses. At the present time we are employing the following in intracutaneous doses in amounts of .02 to .10 cc:

1. Staphylococcus toxoid 1/10 to 1/2 unit doses
2. Mixed respiratory vaccine 1:1,000, 1:10,000 and 1:100,000 dilutions
3. A and B virus vaccines 1:1,000 to 1:100,000 dilutions

These vaccines are being used singly and in combinations. Some satisfactory results have already been noted with the Staphylococcus toxoid and the A and B virus. Further studies, however, must be made before definite conclusions may be reached. The plan is now entirely experimental and is offered as a suggestion to those who wish to try it.

We believe that the ineffectiveness of virus and other vaccines in the treatment of the common cold and pyogenic infections has been the result of the failure to establish an effective optimum dosage. An approach to the problem from this standpoint appears to be encouraging and is worthy of further consideration.

THE PATHOGENIC MOLDS

Although there has been considerable concern in the problem of infections of the nose and paranasal sinuses, now with the use of antibiotics and the disturbance of biotropic balance, the management of complicating fungus infections of the Trichophyton, Monilia, Epidermophyton types, especially the Monilia organisms as they may affect the respiratory tract, introduces a new problem into the field.

In a significant number of cases of dermatophytoses or dermatomycoses of the ear canal, auricle and periocular areas, as well as monilial stomatitis, satisfactory results have been obtained with the intracutaneous injection of a mixture of extracts of trichophytin, oidiomycin (Monilia) and epidermophytin in dilutions of 1:100,000 to 1:100,000,000. Complicating fungus infections either primary or secondary to the use of antibiotics in the mouth, nose, paranasal sinus, or tracheobronchial tree may be controlled by this method of treatment.

ALLERGENIC IMMUNIZATION

In the management of allergic involvement of the upper as well as the lower respiratory tract, the problem of immunization concerns the introduction by injection (sometimes by the sublingual route) of allergenic extracts of dusts, animal danders, pollens, atmospheric molds, pathogenic molds, and other inhalants such as tobacco smoke, orris root, newsprint, et cetera.

Two methods or principles of immunization or so-called desensitization are generally employed. The first method consists in the administration of a series of injections beginning with a small dose, which is usually the end point of reaction determined by serial dilution testing, and gradually increasing the concentration until the point of maximum tolerance is reached. This is determined by the occurrence of an aggravation of the presenting symptoms or a constitutional reaction. This method is based

upon the principle of producing a state of refractoriness to the allergenic substance injected.

The second method of treatment is based upon the principles of the optimum effective dosage. We use this method in preference to the first. As already described, the optimum dosage method is based upon the principle of establishing an effective dosage which is not modified once it is determined. Since the solutions employed are dilute, small amounts of given dilutions are introduced intracutaneously. The amounts vary from .02 to .10 cc. The solutions are serially diluted in multiples of 10. For example, the following relationship is followed:

.02 cc 1:100,000 dilution = .20 cc 1:1,000,000
.05 cc 1:100,000 dilution = .50 cc 1:1,000,000
.10 cc 1:100,000 dilution = 1.00 cc 1:1,000,000

If .01 cc of the 1:100,000 dilution is indicated, .10 cc of the 1:1,000,000 is used, as .01 cc is difficult to measure in a 1 cc graduated syringe.

In the injection of pollen extracts, the initial dosage is usually a multiple of the end point (20 to 50 times). The amount used in testing is usually .01 to .02 cc, so the end point dosage of 20 would be 20 x .01 or .20 cc or 20 x .02 = .40 cc. The 1:100,000 and the 1:1,000,000 solutions are usually employed. The determination of the initial dosage on the basis of serial dilution testing to agents other than pollen has not been consistent and should not be followed as a routine. Instead dosages should be determined on the basis of the clinical picture.

Allergic conditions of the upper as well as the lower respiratory tract are not uncommonly complicated by infection, especially the acute and subacute types. The use of antibiotics and vaccines are usually indicated.

Immunologic therapy may be supplemented in certain cases with ACTH and cortisone or other hormonal therapy (thyroid, estrogenic, androgenic, et cetera). ACTH and cortisone should be used only for the more severe and acute conditions, as relief is not sustained without continued administration.

It is important to recognize complicating infections in order to avoid the use of ACTH and cortisone in its presence.

SUMMARY

1. Immunologic methods in the treatment of sinusitis concern the management of:

(a) Infections
(b) Allergy
(c) Allergy and infection

2. The management of infection concerns the use of:

(a) Vaccines
    (1) Mixed respiratory
    (2) A and B virus vaccines
    (3) Staphylococcus toxoid

(Continued on Page 162)

ALLERGIC ECZEMATOUS SENSITIZATION TO NEOMYCIN

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NEOMYCIN, one of the newer antibiotics with a broad antibacterial spectrum, was isolated by Waksman and Lechevalier[5] from a species of *Streptomyces fradeae*. The efficacy of this antibiotic against *Pseudomonas aeruginosa* suggested its use in those cases of otitis externa in which this microorganism appears to play a role. Falk and Allende[2] reported successful use of an aqueous solution containing 5 to 10 mg neomycin per milliliter, and we[4] also have employed it in such cases with excellent results.

Recently one of our patients developed an acute exacerbation of otitis externa after previously having shown a highly satisfactory response to the use of neomycin ear drops. Upon investigation it was shown that the exacerbation was due to an allergic eczematous sensitization to the drug.

No reports in the literature have come to our attention of cases of eczematous dermatitis of the contact type caused by neomycin used either in an ointment vehicle or in solution.* Neither the reports of Kile, Welsh and McAfee[3] nor of Falk and Allende[2] make mention of cases of proven allergic sensitization to this drug. As a matter of fact, our own experience and that of a number of dermatologists with whom we have discussed this matter indicate that neomycin apparently has a remarkably low sensitizing index. This feature and its very limited usefulness for systemic therapeutic purposes help to make it an excellent medicament for topical use.

CASE REPORT

Mrs. H. I., a middle-aged housewife, complained of oozing, crusting and itching of the ears which had been present for many years and which was sufficiently severe to cause considerable loss of hearing. She had consulted a number of physicians. Therapy had consisted of numerous types of local medications, irrigations with streptomycin solution, and ultraviolet irradiations. Culture of the exudate had revealed *Ps. aeruginosa* and *Staphylococcus aureus*. Cultures on Sabouraud's medium had not revealed the presence of fungi. There had been temporary, but not significant, improvement with some of the local measures. Cortisone, given her by injection, had produced no beneficial effect. An allergic eczematous sensitization to topically applied Vioform had produced a severe exacerbation of her otitis externa.

When first seen by us on May 16, 1951, both conchae were erythematous and scaly. The ear canals were narrowed, the right one almost to the point of complete occlusion, and they showed a yellowish green exudate with erythema, oozing and crusting. The canals were rinsed with 70 per cent alcohol and, because neomycin solution was

*Since this paper was written, our attention has been called to another patient in whom there was strong evidence in favor of allergic sensitization to neomycin; this case is presented in "The Use of Neomycin in Dermatology" by R. L. Kile, E. M. Rockwell, and J. Schwarz, J.A.M.A., 148:339 (Feb.) 1952.

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at that time unavailable, a solution of bacitracin, 500 units per cc in 70 per cent alcohol, was prescibed for local instillation. For itching, Phenergan 12.5 mg tablets were given orally three times daily. After one week there was noted a diminution of itching and lessened discharge from the ears. On two occasions the ear canals were also treated with Thorium X 150 microcuries per cc. On June 1, 1951, neomycin solution became available to us, and the local treatment from then on consisted of ear drops containing neomycin, 5 mg per cc of sterile distilled water, in the morning and continued use of the ear drops containing bacitracin at night. There was sustained improvement, with complete disappearance of itching and substantial improvement in her hearing. She was advised to continue using the ear drops to prevent a recurrence of the eruption.

On October 15, 1951, the patient returned, complaining that her ears again had started to "close up." Moderate itching of the ear canals was present, and there was some discharge noted on her pillow case in the morning, despite continued use alternately of neomycin solution and bacitracin solution. Examination of the canals revealed a recurrence of the swelling and rather marked erythema with slight oozing. Because of the sudden unexplained recurrence of signs and symptoms, an allergic sensitization to one of the therapeutic agents used was suspected. Patch tests with bacitracin solution, 500 units per cc, and neomycin solution, 5 mg per cc, were performed. A papulovesicular reaction was produced at the neomycin test site. The test with bacitracin proved negative.

On the basis of these test results, therapy was continued with bacitracin ear drops and irrigation of the ear canals with saline solution.

COMMENT

Neomycin, an antibiotic with a very wide antibacterial spectrum, is justifiably finding increased use in the topical therapy of pyodermas and certain other infectious dermatoses. One of the distinct advantages of this drug is its apparently low allergenic sensitizing index. Untoward reactions which occur after topical use of neomycin are as a rule due to infection by monilia, which in some cases apparently finds a favorable soil due to the suppression of growth of most of the "normal" bacterial flora of the skin.[1] The case reported here indicates, however, that allergic eczematous contact-type sensitization to neomycin can occur and that such sensitization can take place five months or more after inception of treatment. Sensitization to neomycin should be suspected particularly in those patients in which there is an acute eczematous exacerbation with associated itching occurring one or more weeks after start of neomycin therapy.

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TREATMENT OF ALLERGIC DISEASE WITH A COMBINATION OF ANTIHISTAMINE AND FLAVONOID

Preliminary Report

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IN a very short period of time the antihistamines have become an established part of the allergist's armamentarium. With the rapidly increasing supply of these agents, newer searches include studies of the ways and means to increase the latitude of their usefulness and the safety in their routine administration. The present report deals with a new combination of a selected antihistamine and flavonoid.†

Antihistaminic drugs exert a greater therapeutic effect on seasonal allergies, such as hay fever, than on perennial vasomotor rhinitis. Thenylpyramine hydrochloride has been chosen for this group. It has been reported to give relief in hay fever to the extent of 70 per cent in 112 cases,[1] eighteen of twenty-one cases in Indianapolis,[4] and 76.9 per cent in New York City.[6]

Side reactions are reported for all antihistaminic drugs. The most common untoward effect is sedation, but this varies with the drug, individual response, and dose. Vertigo, dryness of mouth and throat, excitation, insomnia, nausea and vomiting are also reported. With thenylpyramine as with other commonly used antihistamines the incidence of side reactions varies up to 20 to 35 per cent or more.

Flavonoid activity in capillary permeability is well known. It should be of interest in allergy because Vaughn and Black[8] state that ". . . three pathological responses most characteristic of allergy are (1) smooth muscle spasm, (2) increased capillary permeability with resulting loss of fluid into the tissues, and (3) eosinophilia." Capillary permeability is one of the chief problems in allergy.

Although the flavonoids do not necessarily appear to have exactly the effects of the antihistamines, reports in the literature indicate activities in addition to effects on capillary permeability that invite elucidation in the field of allergy, as well as in other fields of medicine. In contrast to knowledge concerning the antihistamines, flavonoid activity is yet vague and toxicity extremely low.

Found in paprika and recognized as a factor in increasing capillary resistance,[7] the flavonoids have undergone close scrutiny for the last decade. Among other properties, these agents are reported to potentiate epinephrine, inhibit spreading effect of hyaluronidase, inhibit succinoxidase, and retard the escape of trypan blue into irritated tissues. Contro-

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†The term "Flavonoid" is used to refer to a group of substances, some of which have pharmacological properties characteristic of vitamin P.[9]

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versy has materialized over reported antihistaminic effects of some of these compounds. For instance, Wilson, Mortarotti and DeEds[10] reported that rutin had a slight though definite action against histamine shock. Subsequently, Raiman, Later and Necheles[5] reported that rutin afforded no protection against histamine shock.

More recently Martin and co-workers[2,3] demonstrated *in vitro* inhibition of histidine decarboxylase, and theorized that the protective action exhibited by rutin in anaphylactic reactions may be due to actual inhibition of histidine decarboxylase.

Preliminary laboratory experiments designed to prove flavonoid activity have been carried out, using excised guinea pig ileum strips, hypotensive effects in the intact cat, and antagonism of toxic histamine injections in the intact guinea pig. Rutin and other selected flavonoids gave results indicating that these agents had enough antagonizing action toward the effects of histamine to warrant further study.

Assuming, in the light of the facts above presented, that a combination of antihistamine and flavonoid might potentiate actions and broaden the usefulness of the antiallergic effects, as well as increase the safety and reduce the necessary dose of antihistaminic agents, preliminary tests were outlined. The present study on combinations of rutin and thenylpyramine hydrochloride was carried out during the last hay fever season. The results warrant a preliminary report. The following formulas* were used:

I. Each tablet contains:	
Rutin	100 mg
Thenylpyramine hydrochloride	25 mg
II. Each tablet contains:	
Rutin	200 mg
Thenylpyramine hydrochloride	50 mg
III. Each tablet contains:	
Rutin	200 mg
Thenylpyramine hydrochloride	100 mg

REPORT OF CLINICAL FINDINGS

In presenting this report of clinical results with the use of a combination of antihistamine and flavonoid, it must be recalled that the particular season** during which the evaluation was attempted happened to be a mild one. However, comparison was attempted between the effectiveness of the antihistaminic agent itself and the combination of drugs. Thus, even though the exposure be small, there must be some correlation between the relief obtained from even minor symptoms by the use of the two medicaments. In no instance was the combination tried where the anti-

*Material was kindly supplied by Lakeside Laboratories, Inc.

**Evaluation was made during the 1950 season, following up flavonoid studies originating in 1946.

TABLE I. CLINICAL RESULTS.
MEDICATION: THENYLPYRAMINE AND RUTIN

Hay Fever				Hay Fever and Asthma				Vasomotor Rhinitis				Urticaria				Eczema			
Total	>	<	S	Total	>	<	S	Total	>	<	S	Total	>	<	S	Total	>	<	S
58	44	4	10	37	26	4	7	15	5	1	9	8	3	2	3	4	1	1	2

>—Greater than antihistamine alone.
<—Less than antihistamine alone.
S—Same.

histamine alone had not been used either previous to or after the administration of the medication concerned in this report.

The choice of rutin in this instance was rather an arbitrary one. It was chosen because of its ready availability, its uses and experience from the standpoint of toxicity, and its relatively low cost.

Seventy-five per cent of the patients felt that there was greater relief from the various symptoms concerned in hay fever, including sneezing, nasal discharge, tearing of the eyes, itching of the eyes, itching of the palate, and itching of the ears, with the combination than with thenylpyramine alone. There was the usual absence of relief in asthma that has been experienced with the antihistamines in general. Approximately 30 per cent of the patients with vasomotor rhinitis reported greater relief with rutin-thenylpyramine than with thenylpyramine alone. In urticaria and eczema there were virtually the same number reporting better relief from both drugs.

All figures shown in Table I are compared to the antihistamine, thenylpyramine, alone. Those who reported both as giving the same result were the same individuals who seemed to get no relief of any sort from either. There was no attempt to evaluate the degree of relief from symptoms other than to compare the medications. Some who reported greater relief of symptoms with the rutin added were only mildly relieved, but with thenylpyramine alone they had no alteration in the symptomatology.

SUMMARY

1. This report shows the comparison between the use of thenylpyramine, one of the antihistamines, and the same drug in combination with rutin, a flavonoid.

2. From clinical observation it is concluded that there is a sufficient increase in the relief of symptomatology with the use of rutin added to warrant further investigation both with this drug and with some of the others belonging to the flavonoid group added to an antihistamine.

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BIBLIOGRAPHY BY DR. JONATHAN FORMAN

A milestone has been reached in the bibliography on allergy compiled by Jonathan Forman, M.D., F.A.C.A., of Worthington, Ohio. Originally, this bibliography appeared in the Letters of the International Correspondence Club of Allergy, founded in 1937-1938. In September, 1950, it was expanded and placed in the *Quarterly Review of Allergy and Applied Immunology*. With the current March issue of the *Quarterly Review*, the bibliography has reached number 10,000. At this point the references will be grouped into Series II, Series III, and so on, each series being numbered from 1 to 9,999.

Doctor Forman is to be congratulated on his bibliography, which is the largest and most complete on allergy being published today.

SOME UNUSUAL EXPERIENCES IN THE PRACTICE OF ALLERGY

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THE practice of allergy today and the practice of allergy in the days when we pioneer allergists were blazing the trail are two entirely different things. From my vantage point of retirement after a lifetime spent in the practice of medicine, twenty-five years of it in the specialty of allergy, I can look back over many unusual experiences. Some of them seem suitable for inclusion in the believe-it-or-not category, but all are taken from actual office records.

First, I might mention pollens. The highest twenty-four-hour count I have ever had verified was one of over 3,000, brought in by a vicious Texas "norther." This count was verified by the well-known botanist, Mr. O. C. Durham. I showed the late Dr. W. W. Duke a similar plate which we simply could not count and which he estimated to be 40,000. These plates were exposed on the roof of a twenty-three-story office building. We no longer see these astronomical counts, as mountain cedar trees, their source, ruin pasturage for cattle, sheep, and goats on nearby ranches, and for this reason hundreds of thousands of them have been destroyed.

The hay fever accompanying such extreme counts is terrific. I have seen hospitalization required, and I remember particularly one boy suffering from hay fever who was brought to the office in extreme anaphylactic shock, with urticaria, angioedema, and tightness in the chest; he was almost pulseless, requiring epinephrine as a life-saving measure—all solely from inhalation of atmospheric cedar pollen.

The youngest asthmatic patient I have encountered was an infant of six weeks; the oldest, a G.A.R. veteran who died in status asthmaticus at the age of eighty-four.

Now for a few brief, unusual case reports.

Case 1.—Seen in 1925 was a woman, aged twenty-nine, who had had six children, five of whom were living. All five of these children at one time or other had had asthma, and when first seen by me, four of the five were actually having asthma. Curiously enough, the family history here was almost entirely negative for allergy, merely a few light attacks of urticaria in the mother of these children.

Case 2.—This patient, a woman in the thirties, when first seen by me was a regular allergy museum. She was actively having, as follows, hay fever, asthma, migraine, urticaria, angioedema, gastrointestinal allergy, and a bilateral hand eruption simulating a severe fungus infection. In addition to polyseasonal hay fever and asthma, she was a highly sensitive primary cornmeal case, one of the very few such I have encountered. It took four months to clear her symptoms. The apparent fungus hand infection was cleared by starvation.

Her family was riddled with allergy; in fact, her father died of asthma.

Presented at a banquet given in honor of the author, Southwest Allergy Forum, April 8, 1951, San Antonio, Texas.
Approved for publication September 6, 1951.

Case 3.—No one thinks of "hives" as doing anyone any good. Yet this particular attack did good, spectacularly. I was called in consultation to one of the local army hospitals to see a young woman for whom two days later there had actually been scheduled a brain operation for intractable headaches. A violent, sudden urticaria was the basis for the consultation, which led to advice to postpone the operation and to institute a few days of absolute starvation. This measure cleared both the urticaria and the current headache. She turned out to be an ordinary wheat cereal case, and she later became one of my technicians. That urticaria was really providential.

Case 4.—Failure of hyposensitization led to the intensive study of this case with its decidedly unusual revelation. Some twenty years ago I was consulted by a bookkeeper in a cotton mill located in Ramos Arizpe, a small town in northern Mexico. His complaint was nocturnal asthma. His skin tests were slightly positive for pollen. We proved this pollen etiology clinically by having him sleep one or two nights in a weed-surrounded tourist court, with resulting asthma, and the next one or two nights in a downtown hotel where there was minimal pollen reception. This was long before the days of pollen filters and antigen-free hospital rooms.

Clinically, this was rather puzzling, in view of the fact that while Monterey, 300 miles south of San Antonio at 1800 feet altitude, is a veritable hot-bed of pollenosis, Ramos Arizpe at over 5000 feet altitude and fifty miles from Monterey has very little antigenic pollen; in fact, many ragweed sufferers secure immediate relief there. The usual factors of bedding and animal hair were ruled out. Studies of his local weeds revealed nothing unusual.

Careful investigation of the house by a very intelligent Dutch-born physician, who was co-operating in this case, revealed that the wife of this patient was a patron of a "curandero" or healer, who was also a dealer in supposedly medicinal herbs to be subsequently imbibed as teas. One of these herbs was the *Franseria tenufolia* form of ragweed, probably secured from Monterey, several bundles of which the lady was in the habit of storing unwrapped in a slatted rack directly over the connubial bed. This is the only patient I have knowledge of who kept ragweed in his bedroom.

Case 5.—This case calls for a little background explanation. The patient was a Mexican lady in the early thirties, a nullipara, evidently of wealth. She and her husband were the type with five or six servants for a family of two. We had dinner later in her home in Mexico City, one of the typical dinners of the wealthy upper class Mexicans of those days, dinner beginning at 9:30 p.m. and lasting indefinitely, with several courses, and a different wine for each course. The lady came to San Antonio to see me about her gastrointestinal allergy and incidentally to do some shopping, or vice versa. During testing, the usual dietary diary was instituted. At the first visit, she told me she was very proud of her figure, and in my opinion, deservedly so. She was willing to go on any diet except one that would make her gain weight.

Subsequent inspection of this diet diary showed among food items a bottle of beer for breakfast, another with lunch, and at least one more bottle with her evening meal. Naturally I explained to her the necessity of some substitution. Two or three days later an inspection of her now amended diet revealed the amazing fact that three times a day she had substituted champagne for beer.

I am sorry that my office has not seen many of that type. Most of our patients belong in the "Coke" economic status.

Case 6.—Seen in 1931, this patient had severe polyseasonal hay fever. A little background is again called for. We have in San Antonio between mid-December and mid-November, with cedar, other trees, grasses, and weeds, some five or six pollen

seasons; and this patient was a victim of most of them. He had paid $250 for an early pollen filter. The machine made so much noise, however, that his wife made him transfer it to the garage. So he charged up the $250 to his profit and loss account, and came to the office. His intradermal tests to the current pollens were positive. Two or three days later, on account of immediate relief, he requested a repetition of the tests. To humor him, this was done. Relief again followed. Our records show that one to four coseasonal intradermal treatments gave this man almost perfect relief for ten consecutive pollen seasons, and he has had very little trouble since. Many allergists have seen this occur for one or two seasons, but for ten seasons, as in this instance, we have, I believe, a record.

Case 7.—This patient, a physician, was a highly sensitive polyseasonal asthma case, ragweed predominating. Because of his country practice, his automobile at times during the autumn was literally covered with yellow ragweed pollen. Years of specific treatment gave no relief to the daily requirements of epinephrine, month in and month out. In fact, he was one of my outstanding failures. Three ant bites incidental to a fishing trip gave him a severe constitutional reaction. Naturally I suggested the dropping of specific therapy. A few weeks ago he told me that for a year and a half since this incident he had been practically free from hay fever and asthma.

The only conclusion I can draw is that there must be somewhere a guardian angel with a special assignment to help out the baffled allergist. No, I do not recommend constitutional reaction therapy for asthma, and I prefer aminophylline and ACTH to ant bites therapy. Another instance of celestial assistance follows.

Case 8.—This is a real puzzler to me from an immunological point of view. This young woman from Houston came over to see me in the spring of 1928, to seek relief from disabling fall asthma of two years' duration. She could always secure relief in Galveston. Her Houston residence was, and is, in a residential suburb. Any Houston allergist will tell you that Houston ragweed seasons are prolonged and intense, and good results from treatment are difficult to secure.

Her initial intradermal tests revealed no unusual sensitivity, merely a 3-plus to a 1:500 Coca solution of giant ragweed. Now, either this case initially was far more sensitive clinically than our tests indicated, or incorrect dosage methods sensitized her. Remember, this was back in 1928. Soon, we had large local arm reactions, at times with a blocked nose, chest tightness, and later urticaria, subsequent to each treatment injection. From the 1:5000 we dropped back to the 1:50,000 and 1:500,000 dilutions, and finally to the 1:5,000,000 dilution, out of which latter dilution we simply could not pass. In other words, our specific preseasonal treatments kept this woman repeatedly on the edge of a severe constitutional reaction, not a very pleasant situation in a patient living some 200-odd miles distant and giving her own injections.

Well, the ragweed season came on as usual, and fortunately specific treatment was stopped before the onset. I figured, rather naturally, that this patient who could not tolerate anything beyond a few hundredths of a cc of a 1:5,000,000 extract hypodermically, stood a good chance of actually dying of ragweed asthma when the pollen season got well under way, and I advised her removal to Galveston at the earliest minimal symptoms.

Much to our amazement, remaining in Houston the entire pollen season, she had neither hay fever nor asthma.

The next year we had sense enough to start with the 1:5,000,000 dilution. Repeated attempts to pass over into a stronger dilution induced the same mild constitutional reaction symptomatology. After several such trials, I threw up my hands in despair and quit. Result again—no hay fever and no asthma.

When in the third year she came for advice, I figured that she was literally too

hot a potato to handle, and that I had had enough. The Lord had undeservedly now been exceedingly good to me twice so far, but there is such a thing as overdoing. So I advised observation, and further treatment only if needed.

We saw this woman, still living in Houston, in the spring of 1945 and again in the spring of 1949 with slight trouble due to house paint and grass. We repeated her skin tests but intentionally omitted ragweed, for fear of disturbing her immunological balance.

This patient, when last seen, had gone twenty years clear of ragweed trouble in a heavy ragweed environment, instead of dying of asthma from that source in any intervening year, as her extreme sensitivity to ragweed extracts would indicate.

Now, I frankly admit that I have made every mistake mentioned in allergy literature, and some not mentioned.

Back in 1920, while I was taking care of a woman patient, her husband, chatting with me one day, remarked that he was manager of a cottonseed oil mill, which he could not enter without having asthma, and that cottonseed meal in bread in the first world war invariably gave him urticaria. Now, in those days, neither I nor anyone else, as far as I know, had ever heard of cottonseed as an extremely potent antigen. So I blithely informed him that I could probably correct this state of affairs. Well, I had his chemist make up an extract in Coca's solution, presumably 2 per cent. Using myself as a control, to rule out any local irritation, and getting none, without the semblance of a preliminary scratch test I gave this man not one but three intradermal tests of this 1:50 extract. The dangerous potentialities of cottonseed and flaxseed are of course well known today.

I had scarcely finished the third injection when things began to happen, and to happen fast. He immediately started nose rubbing and sneezing, with wheezing that progressed almost at once to intense asthma, with urticaria and angioedema that made him look like a poisoned pup. His face grew in a few minutes to what looked like twice its normal size, and one ambitious young allergist literally had the daylights scared out of him. It took what looked like one half the adrenaline in San Antonio to get him out of danger and reasonably comfortable. He declined desensitization.

For some unaccountable reason, in not putting on preliminary scratch or weak preliminary intradermal tests, a few weeks later, I had the same thing happen to an ordinary ragweed grass hay fever patient. It took nearly seven hours of constant attention to get him comfortable. He also declined desensitization.

My early office records fairly bristle with failures due to improper diagnostic and poor treatment technique. It required an abundance of study to get at the bottom of these failure cases. As a matter of fact, our office, for years, actually had the routine custom of treating free of any further financial charges any failure case willing to accept these terms. And believe me, by studying repeated tests and by reconsideration of treatment doses and reactions, we learned plenty. In other words, we pioneers in allergy had to learn by hard, bitter, costly experience.

With excellent postgraduate allergy courses available, with proper methods of diagnosis and treatment available in the literature, with association with experienced allergists in clinics or otherwise also available, it is almost criminal for younger allergists to repeat these errors.

I can remember when pollen filters were unknown, and when pollen surveys were few and incomplete, and when all pollenosis in this country was actually ascribed to ragweeds in the fall and grasses in the spring, and when tree pollen, except for mountain cedar, was unheard of.

I can remember when fungi as specific antigens were considered merely hypothetical possibilities, and when it was heresy to doubt the fallibility of intradermal skin tests as invariable detectors of antigen specificity.

I can remember when we had no eosinophilic nasal smears and when surgery on allergic noses was the rule rather than the exception.

I can remember when I used to sit up night after night with severe status asthmaticus cases, when we had only epinephrine, rectal ether and olive oil, and morphia, long before the days of aminophylline, cases now fortunately much less numerous.

With better temporary control measures, with better material for testing and treatment, with better understanding of the testing needed, and with better understanding of dosage technique for permanent relief, there has been a tremendous improvement in the results of allergy treatment. This betterment, in my opinion, has been due to intensive study of specific diagnostic and specific treatment methods.

While psychic, infectious, and other factors may play a secondary part and of course should be taken care of, my plea to younger allergists, from the very start and forever thereafter, is to classify each and every allergy case without exception as primarily on a specific antigen basis, even if the intradermal tests are entirely negative, and to institute adequate specific therapeutic measures, no matter what the side issues may be.

I have been preaching and practicing this for years, and I feel that my insistence on this point in refractory cases has had a great deal to do with what success my office has had.

Nix Professional Building

KAUFMAN TO SPEAK AT NEW YORK MEDICAL COLLEGE

William Kaufman, M.D., F.A.C.A., of Bridgeport, Connecticut, will give a talk before the Allergy Group at the New York Medical College, Flower and Fifth Avenue Hospitals, on May 6, entitled "Some Allergic Aspects of Arthritis."

THE COMBINED INJECTION OF MASSIVE DOSES OF POLLEN EXTRACT AND ANTIHISTAMINES. STUDY IV.

A Preliminary Report

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IN recent years, attempts have been made to shorten the treatment of hay fever. Loveless[5] presented data to show that satisfactory immunity can be built up by the use of short, preseasonal "booster" courses of pollen extract in patients who, during the previous year, had received the customary, prolonged schedule of treatment. The advent of antihistaminic preparations lent further impetus to this study. Arbesman[1] and Green[4] prevented constitutional reactions during routine hyposensitization therapy by the preliminary administration of an antihistaminic substance. Fuchs[3] was able to give to patients larger doses of pollen extract, about twice the amount usually tolerated, when the antigen was preceded by a dose of an antihistaminic preparation. Maietta[6,7,8] showed that the treatment of hay fever could be reduced to six to eight preseasonal injections and reported satisfactory results in three groups of pollen-sensitive patients when progressively increasing massive doses of pollen antigen were combined with the administration, both orally and parenterally, of antihistaminic agents.

The purpose of this preliminary report is to present another step in advancing the technique of pollen therapy. It essentially embodies (1) the combining of a single large preseasonal dose of pollen antigen and an antihistaminic preparation in the same injection, and (2) the oral administration of two supplementary double doses of the same antihistaminic agent with the preseasonal injection. This technique has been developed over a three-year period (1948-1950) of studies concerned with shortening the treatment period of hay fever. However, it must be emphasized that this method merely points out a promising line of investigation which is still in the experimental stage and is not yet ready for general application.

TECHNIQUE

The study comprised fifty patients who were both clinically and skin sensitive to the pollens of grasses and ragweed. There were fourteen grass-sensitive and thirty-six ragweed-sensitive patients. In addition to the usual scratch tests, each patient, after positive skin tests were interpreted and correlated in the light of the clinical history, was given an intradermal titration test with a test dose of the specific antigen to determine the degree of sensitivity.

Titration of Sensitivity.—Patients were classified into A, B, C and D

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TABLE I. CORRELATION BETWEEN CLINICAL AND TITRATION SENSITIVITY

Titration Class	No. of Patients	Degree of Clinical Sensitivity				Percentage of Correlation
		Severe	Moderate	Mild	Slight	
A (severe)	6	5*	0	1	0	83%
B (moderate)	27	7	20*	0	0	74%
C (mild)	13	4	8	1*	0	8%
D (slight)	4	0	3	1	0*	0%
Total No. Patients	50					

*Indicates correlation between clinical and titration sensitivity

groups by employing pollen test solutions of different concentrations. Patients exhibiting a marked reaction to an intradermal test dose of 1 PU were classified as A or "exquisitely sensitive" (severe); those developing a slight reaction to 1 PU but a marked reaction to 10 PU were classified as B or "average sensitivity" (moderate); those exhibiting a negative reaction to 1 PU but a slight reaction to 10 PU were classified as C or "less sensitive" (mild); and those who were negative to 10 PU but positive to 50 PU were classified as D or "relatively insensitive" (slight). Accordingly, there were six patients in the A group, twenty-seven in B, thirteen in C, and four in D.

An attempt was made to correlate the degree of clinical sensitivity as judged by the patient during previous hay fever seasons and the degree of sensitivity as determined by the titration method (Table I). In the A group, five patients had severe clinical symptoms of hay fever during previous seasons, while one claimed mild symptoms; in the B group, seven had severe pollinosis while twenty had moderate symptoms; in the C class, four had severe symptoms, eight moderate and one mild; and in the D group, three had moderate hay fever, while one had mild symptoms. The percentage of correlation between clinical and titration sensitivity was remarkably accurate in groups A and B. This accuracy was so impressive that it served as a guide or yardstick in determining the massive preseasonal dose for the different classes, because the more severe clinical cases usually cannot tolerate the inordinately large prophylactic doses generally required for the less sensitive patients.

Dose of Pollen Antigen.—The pollen unit dose employed was the Coca-Noon Pollen Unit (0.00001 mg of total nitrogen). Allergenic extracts* of mixed grasses (20,000 PU/cc, composed of equal parts of the pollens of June grass, orchard grass, sweet vernal grass, redtop, and timothy) and ragweed combined (20,000 PU/cc, composed of equal parts of the pollens of common and giant ragweeds) were employed.

Class A patients received 125 PU in a single preseasonal dose. This represents a dose about twenty-five times larger[2] than the initial dose usually suggested for this class of exquisitely sensitive patients. Patients in classes B, C, and D received 250 PU in a single preseasonal dose, which

*Prepared by the Lederle Laboratories, Pearl River, New York.

is about twelve and one-half, five, and two and one-half times larger, respectively,[2] than the doses generally recommended for these classes of patients.

Patients less than 100 pounds in weight, irrespective of the degree of clinical or titration sensitivity, received one-half the above dose of pollen antigen. In these cases, the dose of pollen extract was governed by the amount of antihistaminic medication commensurate with the patient's weight, which, in turn, was deemed adequate to prevent the constitutional reaction which might follow a large dose of pollen antigen.

Dose of Antihistaminic Agent.—Twenty minutes prior to the injection of pollen antigen, 50 mg of Thephorin was administered orally. The injection was prepared by first withdrawing one tenth cc containing the desired amount of pollen units and then 25 mg (1 cc) of Thephorin in an aqueous solution** into the same syringe. A proper mixing of the two solutions was insured by inverting the syringe several times. One hour following the injection, an oral dose of 50 mg of Thephorin was administered. The oral doses of Thephorin were decreased 50 per cent in patients under 100 pounds in weight.

In order to expedite the calculations involved in the withdrawal of both solutions into the same syringe, an elongated 2 cc barrel with a new dual calibration† was employed. On the right side on the distal end, the first cc is graduated in tenths; on the other, both ccs in quarters. Thus, the dose of pollen antigen, in any dilution, being withdrawn first, is measured in tenths; while the 1 cc of Thephorin solution is added by utilizing the quarter cc calibration.

Administration.—The combined antigen-antihistamine injection was administered preseasonally, about seven to fourteen days before the onset of the specific season. Injections were given subcutaneously, about three or 4 inches above the elbow on the lateral surface of the arm. The usual precautions against back seepage were observed.

PHARMACO-IMMUNODYNAMICS

Pharmacodynamics.—A massive dose of pollen antigen ordinarily may produce a constitutional reaction in a patient specifically sensitive to it. However, a patient adequately protected by an antihistaminic agent appears to tolerate an inordinately large dose of pollen without an untoward reaction.

Thephorin, an antihistaminic preparation, "inactivates or neutralizes" some "general-reaction-producing substance," probably closely allied to histamine or H-substance, produced locally by the massive initial dose of pollen antigen. With the combined antigen-antihistamine technique, the

**Prepared for this study by Hoffmann-La Roche, Inc., Nutley, New Jersey.
†Supplied by Becton, Dickinson & Co., Rutherford, New Jersey.

primary perimeter of inactivation is local, at the site of the injection. There, the parenteral antihistamine does not retard local absorption of the pollen extract but, being deposited well in advance of the release of the "general-reaction-producing substance," inactivates the histamine-like substance as it is being released from the tissues. The secondary perimeter of inactivation is in the blood stream close to the cells of the shock organ where the ingested antihistamine is circulating following its absorption from the gastric mucosa and where any excess of histamine-like substance, absorbed from the local reaction, is neutralized.

Immunodynamics.—The prophylactic administration of an antihistaminic preparation combined with massive doses of pollen antigen does not inhibit the formation of protective or blocking antibodies. During the 1948 and 1949 hay fever seasons, Maietta[7,8] reported excellent results in 110 patients who received preseasonally six to eight progressively increasing massive doses of pollen antigen simultaneously combined with the administration of antihistaminic preparations. During the 1950 hay fever season, a single massive preseasonal dose of pollen antigen, administered seven to fourteen days before the onset of the specific season, was large enough to stimulate an adequate protective or blocking antibody response which lasted throughout the specific season. The formation of this protective mechanism did not appear to be inhibited by the simultaneous administration of the antihistaminic agent.

The dynamics appear to be twofold: (1) the pharmacologic action of the antihistaminic preparation prevents a constitutional reaction by inactivating the "general-reaction-producing substance" which may be released by the excessive dose of pollen antigen, and (2) the large pollen dose, uninhibited by the antihistamine, stimulates the formation of sufficient protective antibodies to confer adequate protection throughout the season.

RESULTS

Fifty clinically sensitive pollen patients (fourteen grass and thirty-six ragweed) received a single preseasonal antigen-antihistamine injection. There were thirty-four females and sixteen males. Their ages ranged from nine to fifty-four years. Two patients weighed less than 100 pounds. All lived in the Greater Boston area, pursued their usual daily routine, and took no medication during the season. Each patient kept a clinical diary during the season and tabulated his own result daily. These were graded excellent (completely symptom-free); good (mild, fleeting symptoms during the peak of the season only); fair (mild symptoms appearing intermittently throughout the season), and poor (symptoms requiring medication during the season).

Side Reaction.—Considering the inordinate amount of Thephorin administered with each injection within one hour and twenty minutes, side effects were relatively mild. Seventeen patients (thirty-four per cent)

complained of side reactions. These symptoms were inconsequential and fleeting and included insomnia, jitteriness, drowsiness, and fatigue.

Local Reaction.—Locally, slight itching, burning, or stinging generally accompanied an injection. These symptoms were transient and disappeared within a few minutes. The local reaction was delayed in the majority of the cases, varied from 2 to 10 cm in size, and lasted from a few hours to thirty-six hours. Local tissue edema was proportionate to to the size of the reaction.

Absence of Constitutional Reactions.—Despite the massive pollen dose, not a single constitutional reaction occurred.

Clinical.—Nineteen patients (38 per cent), seven grass-sensitive and twelve ragweed-sensitive, had an excellent result and remained completely symptom-free throughout the season; twenty-three (46 per cent), six grass and seventeen ragweed, had a good result and exhibited mild, fleeting symptoms at the peak of the season; six (12 per cent), 1 grass and five ragweed, had a fair result with mild symptoms occurring intermittently throughout the season; and two (4 per cent) had a poor result. The latter, both ragweed-sensitive patients, had a good hay fever season but developed acute bronchial asthma at the height of the season.

Fourteen grass-sensitive and thirty ragweed-sensitive patients had received desensitization therapy the previous year, and for these cases the single injection of pollen extract may have acted as a "booster" treatment. The remaining six patients, all ragweed-sensitive, had had no previous desensitizing therapy; of these one had an excellent result, three good, and two fair.

The encouraging results in this limited study must be evaluated in the light of the following facts. Greater Boston is a low pollen count area and hence the single dose that would give relief to patients in this vicinity would not necessarily do so in a high pollen area. Grass pollen cases yield to therapy much more easily than ragweed pollen cases. Further, it is known that a number of patients can take large doses of pollen extract safely, although not protected by antihistaminic or other agents. Finally, it is also known that there are a certain number of patients who with single injections of pollen extract frequently do well.

COMMENT

From a medical viewpoint, the single injection treatment of hay fever, although still experimental, is a possibility. With the combined antigen-antihistamine technique, the single preseasonal injection apparently is a safe, practical procedure. The massive pollen dose administered appeared to be the optimum dose. It stimulated the formation of sufficient protective antibodies to confer an adequate degree of protection throughout the

season in the majority of the patients. The dose of the antihistaminic agent was large enough to prevent a constitutional reaction yet was attended with minimal side effects in a few patients.

Aside from the above, the single injection treatment of hay fever has several other advantages for the patient. It is economical, convenient, and preferred to a multiple dose schedule. Further, it encourages more patients to seek specific treatment yearly and, because of its safety and simplicity, may discourage self-medication with antihistaminic drugs.

SUMMARY AND CONCLUSIONS

The single injection treatment of hay fever, combining the simultaneous administration of a large dose of pollen antigen and an antihistaminic substance, has been presented. The method, still in the experimental stage and not yet ready for general application, points out a promising line of investigation. Of the fifty pollen-sensitive patients receiving this prophylactic treatment, nineteen had an excellent result, twenty-three good, six fair, and two poor.

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482 Beacon Street

The College welcomes a new sustaining member, Allergy-Free Products, and invites readers to peruse the advertisement on page xl. The firm is managed by Mr. and Mrs. M. G. Gray, 1431 N. Broadway, Springfield 1, Missouri.

EFFECT OF BACTERIAL ANTIGEN PLUS ANTIBODY ON BRONCHIAL ASTHMA

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WHILE in China over twenty-five years ago, the writer became greatly interested in the relationship of bacteria to allergy, having cleared up a number of cases of asthma by giving inoculations of bacterial antigen plus antibody. Returning to Canada, he observed the case of a sixty-year-old man whose twenty years of purulent bronchitis and asthma suddenly ceased after three such inoculations. The interest thus aroused resulted in further study. This paper attempts to report the results of twenty-five years' experience of treating bronchial asthma with bacterial antigen plus antibody (called by the manufacturers "sensitized vaccine" or "serobacterin").

Beginning with doses recommended by the manufacturers (much too small to obtain maximum benefit in most cases) it took some ten years to discover the proper average doses. These may seem very large to those unfamiliar with the product, but many who have followed the writer's advice to give adequate dosage boldly have verbally reported excellent results, similar to those described here. On the other hand, some who have attempted treatment with considerably smaller doses and much smaller increments have told the author that a considerable percentage of their patients suffered quite severe local or general reactions.

It must be emphasized that serobacterins differ from all other bacterial vaccines, containing antibody as well as antigen. In the case of the respiratory mixture, the first dose represents 1400 million killed bacteria, including seven different kinds, or a little more than the last dose of most standard vaccines. To equal the sixth dose one would need to give about 15 cc of a standard stock vaccine. A brief statement concerning the product and the author's method of using it is appended to this paper, and has been published earlier.[2] There is no *serum* in sensitized vaccine.

There are no contraindications for sensitized vaccine, and it is assumed in this discussion that palliative treatments are given to asthmatic patients as and when required for relief.

The victim of asthma practically always states that he receives some benefit from a course of the respiratory serobacterin mixture given as described later. Even those cases who show several to numerous positive skin tests, but are not completely relieved when they avoid the substances concerned, frequently lose their wheeze entirely or state that it occurs less often and less severely after such treatment. Most of the following types of cases also give objective evidence of improvement following sensitized

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vaccine therapy: (1) Children whose attacks of asthma always follow a cold. (2) Children whose *first* attack dates from an acute respiratory condition such as bronchial pneumonia, measles, or whooping cough. (3) Adults whose first asthma occurred during or soon after an acute respiratory infection such as pneumonia or sinusitis. (4) Adults with clinical signs of chronic sinusitis, whether they have x-ray findings or not.

This may seem to include nearly all cases of asthma. As a matter of fact, for a good many years instead of first using every other type of investigation and treatment (with benefit to some) and finally wondering if the resistant case is one of so-called "infective" asthma, the writer has reached the point of treating every case as having at least an element of immunity reaction or sensitivity reaction (or both) against bacteria. By raising immunity or decreasing sensitivity (or both) at least one source of sensitivity reaction is lessened. It is most surprising how few cases need further investigation or treatment!

It is true that all cases are not benefited alike. It is also true that on rare occasions one is confronted by an impatient patient who has some major allergen other than bacteria, which a careful history and observation did not reveal, but which somebody discovers for him by doing a series of skin tests! On the whole, however, it seems to this writer that one will control more cases of asthma more rapidly by treating the bacterial element first and then carrying out other procedures if and as required. Often nothing further is required!

Does this sound irrational? Try to find anyone whose respiratory tract (particularly the sinuses) does not contain numerous bacteria, and who is not constantly breathing in more bacteria from the air of rooms in which people have lived—bacteria which not only add to the bacterial antigen already present, but which can take the material of the host's own cells and fluids and change it to proteins or toxins to which the host's tissues *may* be hypersensitive! No matter what other allergen may be involved, is it not a rational procedure to attempt to insure that such a hypersensitivity to bacteria and their products shall be at a minimum, not *after* we seek for and try to eliminate other influences, but before or during such a study? In practice such procedure gives good and sometimes dramatic results, especially in the four types of patients already mentioned.

1. In children whose asthma always follows a cold, the action seems to be twofold. Even in nonasthmatic children the incidence of the common cold is greatly reduced and often eliminated by adequate treatment with sensitized vaccine. Attention has been called to this in a previous publication.[1] Not only are the bacterial sequelae prevented, but the individual seems to be actually less susceptible to the initial virus cold. But in the asthmatic child, even before the patient's resistance is built up to the point where he does not have some colds, parents often note that the cold is not accompanied by an asthmatic attack. Consider two examples:

J. S., a young man of about twenty-one years, recalled in the summer of 1950 that when he was about three or four years old he had a great many colds and asthma until he was given a course of sensitized vaccine. He has been free of asthma and practically free of colds ever since.

W. F., a boy, aged six, whose father is asthmatic, was brought to a medical clinic August 20, 1949, having had frequent colds, mouth breathing, and heavy breathing at nights for over a year. He received palliative treatment until May 17, 1950, when he was admitted to the pediatrics ward because asthmatic attacks were becoming worse. Sensitized vaccine gave marked improvement, and he was discharged on June 13. One attack of respiratory infection with some asthma in the winter of 1950-51 improved rapidly with another course of serobacterin. He is still well early in 1952.

2. Children who begin to have asthma following an acute respiratory condition usually have evidence of chronic sinus involvement, such as nasal congestion, lack of voice resonance, postpharyngeal drip, history of tonsillectomy and adenoidectomy, and history or presence of some degree of otitis or mastoiditis. The writer has reported previously[2] the tremendous value of treatment with sensitized vaccine in chronic sinusitis, and his clinical impressions have by now been corroborated through personal communications from a considerable number of allergists and general practitioners who are using the method with success. It seems that the sinusitis is the chief cause and source of the asthma in the type of children being considered, because clearing up the sinusitis is usually followed by long periods of relief from asthma, and this even in children who are definitely known to be allergic to other respiratory allergens.

E. K., a ten-year-old boy had had intervals of cough, wheezing, and choking at nights for two years, had had sinus trouble since about four months old. He had had a tonsillectomy done on account of sore throats, blocked nose, and frequent head colds. Lately he had had headaches, dizziness, and feeling of eyestrain. Soon after the asthma began some skin tests had been done. A course of sensitized vaccine was begun October 6, 1949. He improved steadily, so that on December 13 his eyes, nose, and breathing were much better. With monthly inoculations he had only one or two very slight asthmatic attacks between that date and August, 1950, when he had some attacks of wheezing in the evenings. Another short course of sensitized vaccine extending over about three weeks cleared this up again.

3. Similar theory and practice seem to apply to adults, some of whom can definitely date their first asthma as having followed an acute respiratory infection and others who have the clinical sinusitis already mentioned. The following case report illustrates but of course does not prove what can be done for these unfortunate individuals.

Mrs. A. M., aged fifty-nine, by July 22, 1950, had had asthma for nearly twenty years with practically continuous wheeze of late. She thought she had not recovered from an acute cold the preceding autumn. About four years ago polyps were found and removed by a nose and throat specialist who found her skin-sensitive to dust, feathers, dog hair, and wool. She was given inoculations against dust, feathers, fur, and wool combined with "cold serum," with benefit for a time; but when given

inoculations last autumn she got severe reactions. She has also been seen since by a general practitioner and a psychiatrist. The sputum is yellow and the patient emphasizes the element of "a severe cold." She improved rapidly on sensitized vaccine and was feeling much better in a month, being improved in all ways. At the end of two months she was doing her own housework for the first time in years. Fifteen months after beginning treatment she was still not having asthma, although at that time she had contracted a slight head cold.

It must be understood that it is not necessary to have evidence of antecedent or concurrent bacterial infections in an asthmatic patient, in order to arrest the allergic manifestations. Witness the following two case reports which represent widely varying ages.

D. M., a fourteen-month-old boy seen October 18, 1949, had had a tendency towards asthma since birth, becoming quite wheezy at times. He had been worse for last two weeks on account of an acute cold. The condition cleared up with three inoculations of sensitized vaccine. His mother reported a year later that he had been free of wheezing, even on two occasions when he had slight colds.

Mrs. J. C., seventy years old, reported on June 20, 1949, that she had begun to have attacks of wheezing about ten years ago. Now she gets one about once a month, lasting nearly a week. She is quite well in between attacks. No special lead could be discovered as to allergens concerned, and there was no obvious respiratory infection, but she had considerable pharyngeal dropping. She began to feel very much better after two inoculations of sensitized vaccine, and after one or two very slight attacks of wheezing she stopped having attacks and described herself as being the "best in a long time."

Case reports prove nothing but may serve as clues to useful methods of treatment. The following three illustrate how one can successfully treat many asthmatic patients without any preliminary testing, but are not intended to indicate that the method yields 100 per cent perfect results.

A sixty-six-year-old man who had had chronic bronchitis for many years, with shortness of breath and wheezing at night, improved gradually with serobacterin until in six weeks he was able to sleep well and carry on outside activities without discomfort. Eight months later he was still well.

On his recommendation a woman of forty-four who had had shortness of breath for nineteen years, at first only in attacks but of late more frequently, came in for treatment. She also had some degree of summer pollinosis. Under treatment with serobacterin she improved rapidly until she had no wheezes, had "better wind," and needed no palliative drugs.

She was so pleased that she induced a woman of thirty-two, who had been having attacks of asthma and shortness of breath since she was five or six years old, to come for treatment. This patient had two uncles who were asthmatic. She improved greatly on serobacterin, and in three weeks "did a washing," an activity she could not do previously. In two months she reported she was "the best in several years."

TREATMENT

Product: H. influenzae Serobacterin Vaccine Mixed (No. 4750) Sharp & Dohme.

Give subcutaneously at interval between doses of three to seven days, not over one month. Divide doses over 1 cc, giving half in each of two places.

Local reactions one or two inches in diameter are usual. If excessively large or much muscle soreness occurs, repeat that dose before giving larger ones.

General reactions are rare, but sometimes beneficial, and should be followed by the same or a smaller dose.

The following are doses which are ordinarily tolerated by adults and children alike:

0.2 cc; 0.4 cc; 0.8 cc; 1.2 cc; 1.8 cc; 2.5 cc

The 2.5 cc doses should usually be repeated several times at intervals of one to three weeks. In a few intractable cases good results are obtained only by giving doses of 3 cc.

SUMMARY

Increasing doses of a mixed bacterial antigen plus antibody, up to fifteen or twenty thousand million killed bacteria, will give *some* relief in *nearly all* cases of bronchial asthma, and when bacteria are more obviously concerned usually gives such complete control that no more complicated study or treatment is required. The author therefore suggests that this should become the standard *first* line of treatment in all cases, to be followed by or associated with other procedures only when it fails to give complete relief.

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562 Dunn Avenue West

COMMON COLD CONFERENCE

The Common Cold Foundation sponsored a conference on the common cold, February 13, in Chicago, Illinois. Dr. Thomas G. Ward, Associate Professor of Bacteriology at Johns Hopkins University, was guest speaker at the conference, and his talk was followed by a panel discussion. More than fifty-five important industries in the Chicago area were represented by their medical directors, personnel, industrial and public relations officers, and industrial nurses. The role of the common cold in economic loss to industry and business, the dangers of its complications, and the lack of continuous research on the common cold, which causes more disability than all other diseases combined, were emphasized.

SUCCESSFUL TREATMENT OF ECZEMA OF THE EAR CANAL

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ECZEMA of the ear canal has been an extremely difficult problem to both otolaryngologist and dermatologist. The situation to date has been well stated by Cornbleet and Schorr[5]: "Itching with and without evident dermatitis of the ear canal is a common complaint. Like some other frequent disorders, such as the common cold, its cause is the subject of debate. The many forms of treatment recommended merely attest to the indifferent results following them. . . . In recent years there has been increasing doubt as to the pathogenicity of the various aspergilli, penicillia, mucors, yeasts, and various fungi found associated with eczema of the ear canals. This has been counterbalanced by a growing belief that it is the bacteria found there that are more likely to be at fault. It is now commonly thought that fungi in the ear canals are harmless contaminants, growing easily on suitable soil present there."

To judge by various articles on the subject and the types of treatment most used at the present time, we must conclude that most otolaryngologists and dermatologists believe that this intractable condition is due to the actual presence of bacteria in and on the skin of the ear canal. Various powders and ointments containing sulfa, penicillin, aureomycin, or some even more recent antibiotic, are being used a great deal with the idea of discouraging the growth of the guilty organisms. In some cases, however, a sensitivity reaction to the local application has made the condition more severe. In the minds of the present authors it is necessary to go one step farther and realize that the real difficulty lies in the "changed capacity to react" of the skin cells in the area. In other words, the condition is fundamentally a sensitivity reaction of the skin, very frequently, but probably not always, due to products of bacteria. It is not necessary, however, for the bacteria to be actually at the site of reaction. They may well be located in some such focus as the sinuses,[3] a tooth root, a throat which is not even sore, or as far away as the intestine.

The idea that certain dermatoses are probably due to allergy to bacteria and their products and can be successfully treated by large doses of bacterial antigen plus antibody has been discussed by the senior author in previous publications.[2] New and corroborative evidence has been accumulating in the last year or two.[4] The method has been used by other workers who have privately reported good results in eczema-dermatitis, psoriasis, pustular bacterids, and various erythematous and papular eruptions, where obvious allergens have not been discovered. Certain investiga-

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tive work seems to support the viewpoint that these conditions can be due to sensitivity to the products of bacteria: notably the work of Storck of Zurich[7] and Norrlind of Sweden.[6]

The present paper is intended to report a small group of cases of eczema of the ear canal in which the method of treatment by antigen plus antibody has proven successful, in some cases after standard local treatment had failed. So few cases prove nothing but do indicate a more promising approach to this problem than any other which is known to the authors, who feel that it should be better known to all those who have to deal with otitis externa. It applies equally well to those cases in which the eczema affects only the auricle, without reaching into the canal; one or two cases are presented to illustrate this. Eczema behind the ears should probably be omitted from this discussion, although it too responds. The problem of recognizing psoriasis of the ears, raised by Cornbleet and Schorr, need not arise because about 90 per cent of cases of generalized psoriasis seem to respond to the treatment suggested.[4]

The following is a brief and dogmatic statement of the method of treatment:

As in eczema in other areas, local treatment should be soothing, and accumulated secretions removed as gently as possible.

Where there is evidence of upper respiratory infection use *H. influenzae* Serobacterin Vaccine Mixed (No. 4750, Sharp & Dohme). Otherwise use Staphylo Serobacterin Vaccine Mixed (No. 4822, Sharp & Dohme).

Allow three to seven days between doses. It is safe to give an increased dose at any time up to four weeks. After that many patients seem to lose their tolerance quite rapidly. If a patient reports a general reaction or marked local reaction, it is best to repeat the causal dose or even to give one slightly smaller.

Most patients can be given the following doses *subcutaneously* (never intramuscularly) with no marked discomfort:

0.2 cc; 0.4 cc; 0.8 cc; 1.2 cc; 1.8 cc; 2.5 cc

The last dose often needs to be repeated at intervals of one or two weeks to get complete cure. A few need doses of 3.0 cc. Infants and children tolerate the same doses as adults. When the dose is over 1.0 cc, it is well to give one half in each of two places.

It is possible in many cases to obtain good results with doses of a much smaller order than those suggested. For example, in cases Mrs. O. and Mrs. M. mere repetition of one tenth the initial dose suggested seemed to satisfactorily alter the reaction of the skin of the ear canal. On the other hand, conversation with various workers who have used sensitized vaccines in various ways gives the impression that fewer excellent results and more unpleasant reactions follow the use of small doses than come after those stated. Much work remains to be done in discovering optimum dosages, but it is suggested that the schedule given is a very efficient one.

M. S., a young woman of seventeen years, reported on August 24, 1950, with a crusty eczematous condition around the orifice of left ear and behind it, with some

discharge from the canal, and an area of dermatitis on each side of the chin. The condition had been present for about a month. An intern had given her unguentum hydrargyri ammoniatum and told her to use hot boracic compresses. On September 7 the condition was about the same. A soothing ointment was prescribed and inoculations of Staphylo Serobacterin Vaccine Mixed were begun. The condition was so much better by September 14 that she had stopped local applications. The third inoculation was given. When she returned to the clinic on September 28, the ear was cleared.

Mrs. M. W., thirty-two years old, stated that five days after extraction of a lower tooth the right ear canal began to discharge and feel sore. Five days after, on September 7, 1950, she was given a soothing ointment and 0.2 cc Staphylo Serobacterin Vaccine Mixed. That night she developed marked periorbital swelling and was admitted to hospital and treated with intramuscular penicillin as a case of cellulitis. The writer considers that this diagnosis was in error, since the temperature was normal during her five days in hospital. The condition was probably an extension of the allergic dermatitis of the ear canal. She also had an eczema-like rash on flexures of elbows. All three areas cleared up quite promptly. On September 21 the ear canal appeared normal and remained so.

R. McC., a young man of twenty-eight years, had had a red and inflamed eczema-dermatitis of the ear canal, sometimes extending to the outer ear, for a number of months. He had been treated at a D.V.A. hospital by an otolaryngologist and seen once or twice by a dermatologist with no particular improvement in the condition. Treatment with *H. influenzae* Serobacterin Vaccine Mixed for an acute cold was begun December 23, 1949. The cold improved rapidly, and without any local treatment whatever the ear canal had become normal when seen on January 5, one week after the third inoculation.

In early July, 1950, this patient developed another acute head cold, and both ear canals were becoming itchy, with some "pink" serous discharge. He was given medicated glycerine ear drops for use in the canals and a mild soothing ointment for use around the orifices. A course of inoculations with Staphylo Serobacterin Vaccine Mixed was begun on July 8. By July 22 the condition was greatly improved. On that date he received a fifth dose of 2.0 cc of the vaccine, and the condition went on to complete recovery.

E. H., a man of thirty-two years, noticed early in October that his right ear began to develop a scabby area near the orifice. This spread, and on October 12, 1950, he consulted an otolaryngologist. In spite of treatment, the rash spread over face and body, so he was referred to a dermatologist. He was treated for eight days in hospital with local therapy including streptomycin ointment to the ear, with Benadryl, and with intravenous triple typhoid therapy which produced considerable reaction with chills and temperature of 103° to 104°. The latter treatment was followed by swelling of the face and upper chest and then some peeling. The skin seemed better and drier.

When the patient was first seen by the author, January 5, the rash had been breaking out again. He had scattered moist spots on his face, some in the scalp with crusts, and facial skin much irritated by shaving; the ear canals were mildly inflamed, somewhat cracked, and showing discharge in the mornings. He had a considerable amount of pharyngitis. He was given a soothing ointment and inoculation of *H. influenzae* Serobacterin Vaccine Mixed. Three days later his ear orifices were smoother and drier and were showing no morning discharge. Other affected areas of skin looked better and he said he felt better. He was given a second

inoculation and returned eight days later markedly improved in all ways. He did not continue treatment, relapsed, and is still seeking relief from various sources, six months later.

Mrs. G. W., thirty years old, in October, 1949, pricked her scalp with a hatpin and developed a rash, which spread out from the point of injury until it covered much of her face and neck. She was referred by her obstetrician to a surgeon who treated her until about March, when she consulted a physician who cleared up much of the rash with moist compresses and intramuscular penicillin. During this latter treatment, which was carried out in hospital, the right ear canal became affected and gave considerable trouble.

In June, 1950 (some eight months after the original injury), the physician referred her to an otolaryngologist who treated her for more than two months. At various times he used penicillin, silver nitrate, and aureomycin powder locally. The latter seemed to benefit the condition at first but later caused reaction in the ear canal. Finally, aureomycin by mouth seemed to cause some enteritis and was followed by the development of a slight new rash on her face and scalp. This began to clear up when the aureomycin was discontinued.

When seen on August 29, 1950, this patient was using cotton plugs to blot up the serous discharge from her ears. A course of Staphylo Serobacterin Vaccine Mixed was begun and no local application employed. Three days after the first dose there was considerable improvement; and on September 5, four days after the second dose, the ear was drier, although discharging somewhat at night, and the patient stated that she felt it was much better. On September 18 the ear seemed to be very nearly normal. This continued to be true until October 2, when the patient developed an acute head and chest cold accompanied by some fresh irritation of the affected ear canal.

Throughout October and November this patient was given large doses of Staphylo Serobacterin Vaccine Mixed once each week. Gentle mechanical cleaning of the ear canal and use of soothing ointment and glycerine drops was recommended. Although the condition was much improved compared to what it had been in late October, there was still an area of irritation and weeping with some swelling just around the orifice. On November 23 she was told to use an antihistaminic ointment (Thephorin) for two days only. There was rather dramatic clearing up of the residual irritation so that when seen on December 7 the ear and its canal seemed to be perfectly normal.

Mrs. O., fifty-three years old, for two years had scaliness behind the ear and external otitis with considerable crust formation and discharge. She was treated with injections of 1:10 dilution of Staphylo Serobacterin Vaccine Mixed, 0.2 cc every five days. After six injections she was completely clear of eruption.

Mrs. M., thirty-three years old, for one year had had scaliness of the scalp with loss of hair, and a serious external otitis, watery in type, in both ears. She was treated the same as Mrs. O., and after twelve injections the external otitis and scaliness cleared and the hair was returning normally.

S., a twenty-eight-year-old man, had had an external otitis in the left ear for about a month. There was a foul-smelling discharge. He was treated with *H. influenzae* Serobacterin Vaccine Mixed, beginning with 0.2 cc. By the sixth injection of 1.2 cc the ear was dry and remained so.

C. V., a fourteen-year-old girl, reported on November 3, 1950, with discharge from ears and auricles and behind both ears since August. She showed evidence

of chronic pharyngitis and sinusitis. She was advised to use boracic compresses for the weeping, and was given soothing ointment and a course of *H. influenzae* Serobacterin Vaccine Mixed. She was almost well in six days, after two inoculations. After the third dose given on November 9, she had a slight general reaction and a slight flareup of the rash, so the same dose was repeated on November 16 with prompt improvement. By November 30 the ears were normal.

W. C., a man, thirty-three years old, stated that both ears had been swollen and inflamed for two months, with some burning and itching. He had been seen and advised by four general practitioners before consulting the authors. At that time, September 28, he was using a proprietary salve which gave some comfort. He was advised to make no change in local treatment, and a course of Staphylo Serobacterin Vaccine Mixed was begun. The ears were improved in appearance and not so itchy by October 6, four days after the second dose. Thereafter no local treatment was used, but the inoculations were continued. On November 13, two weeks after the seventh dose, the ears were considered to have returned to normal.

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METHODS OF IMMUNIZATION EMPLOYED IN THE TREATMENT OF SINUSITIS

(Continued from Page 135)

(b) Antibiotics
  (1) Penicillin, aureomycin, chloromycetin, terramycin, et cetera
  (2) Sulfonamides

3. Allergic management includes immunization to:

(a) Pollens
(b) Dust, animal danders, atmospheric molds
(c) Foods (sublingual)
(d) Hormonal Therapy
  (1) ACTH and cortisone
  (2) Thyroid, estrogens, androgens, et cetera.

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ALLERGY IN RELATION TO PREVENTION OF "COLDS"

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DURING the first twenty years of our research into both treatment and prevention of "colds" in the Student Health Service at the University of California and in private practice, the problem of allergy (chiefly hay fever and asthma) entered the picture so frequently that a study was finally made in an effort to clarify the importance of allergy in relation to "colds" of all sorts. Consideration was given not only to incidence of allergy but especially to treatment of this specific condition.

The incidence of allergy in a group of 2,380 students were as follows:

Hay fever (known)	343
Asthma (known)	75
Family history hay fever or asthma	340
Total	758

Thus, allergy had to be considered as a factor in susceptibility to "colds" in approximately 33 per cent of the students, studied from this point of view. Whenever the symptoms, or family history, suggested allergy, review and treatment by the allergist, as well as by the nose and throat specialist, was instituted.

Agreeing with Feinberg,[2] Urbach and Gottlieb,[4] Rowe[3] and allergists in general that allergy alone may set up an irritation in the nose and sinuses and bronchial tubes, similar in many ways to the defense reaction to infections in the same areas, it is obvious that allergy must have front rank consideration in any program to avoid "colds."

The physician who must determine first whether allergy is present usually requires the aid of both the nose and throat specialist and the allergist. He will need to know whether he is dealing with a pure allergy, without any infection, or whether he is dealing with both allergy and susceptibility to infections, both of which require treatment. Examples of each will clarify this point.

PURE ALLERGY CAUSING "COLDS"

Case 1.—L. C. T., aged eighteen, had had mumps at twelve years but no other infection, except colds. Always a city dweller and hence exposed excessively in crowded public schools, nevertheless he had experienced almost no infections, indicating an excellent natural defense apparatus. However, there was a history of susceptibility to "colds" all his life, their greatest frequency being in spring and early summer, the average being six "colds" a year. Thus he exceeded the majority (none to three "colds" a year) in number of "colds," but in eighteen years had experienced far fewer than the average number of infections (the average in our students' eighteen years of age was measles, mumps, whooping cough, chicken pox, influenza or perhaps one other of the more severe infections, such as scarlet fever).

A history of asthma since the age of five and suspected hay fever since the age

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of ten made it certain that we were dealing with allergy. Routine allergy work-up with skin testing demonstrated positive reactions to English rye grass, red top, and orchard grass, and also to house dust.

General Physical Examination: Normal throughout.

Specialists' Reports: Ear, Nose and Throat Department: A nasal spur not large enough to obstruct the airway or prevent sinus drainage. No rhinitis (examination made in the autumn when he was free of hay fever). Tonsils absent (it should be noted that removal of his tonsils in childhood had not reduced the number of "colds").

Laboratory Tests: Urine normal. Kline negative. Tuberculin P.P.D. No. 1. The patient reported no redness or swelling appeared at site of test.

Treatment and Outcome: Following the allergy tests in April, 1939, a course of injections was given: pollen and house dust antigen and a routine series of Cutter M.V.R.I. No. 4 count mixed respiratory bacterial vaccine.

Observation from August, 1939, to August, 1941, showed no "colds" observed or reported. It is reasonable to conclude that treatment of the known allergy prevented the frequent and seasonal *allergy "colds,"* while a single routine course of mixed respiratory bacterial (Cutter) "cold" vaccine was sufficient to raise the defense against prevailing acute respiratory infections. This patient might have gotten along quite well on injections of pollen and house dust alone, but a perfect result was assured by including vaccine.

ALLERGY AND POOR NATURAL RESISTANCE TO INFECTION

The problem is entirely different when the patient has both allergy and poor natural resistance to infections, failure or incomplete success resulting from treatment, however good, for either condition alone. The following case history illustrates the success that attends combined treatment.

Case 2.—B. M. S., aged eighteen, had had hay fever and occasional asthma all his life. In addition, his record included mumps at seven, whooping cough at seven, measles at nine, German measles at seventeen, acute mastoiditis with operation at ten, and recurrent mastoiditis since. He had averaged four colds each year.

Specialists' Reports: Ear, Nose and Throat Department: A deviated septum without obstruction. Chronic rhinitis (allergic). Mastoid pathology with moderate deafness. Tonsils absent.

Laboratory Tests: Urine normal.

X-Rays: Mastoids—almost complete absence of cells on the right side, probably due to old sclerosis, and a few large cells on the left covering a very small area, which seems normal. Chest—no x-ray evidence of an active lesion. Mild tracheobronchial lymph node calcification. Heart and aorta normal.

Treatment and Outcome: Our observation covers six years from August, 1935, to August, 1941, and falls naturally into three parts.

The first three years (1935-1938) were completely unsuccessful because treatment was given only when a "cold" occurred, i.e., in the nose and throat department, if mild, or admission to the medical service of the hospital, if severe and prostrating. The record shows the usual number of "colds" of the usual severity and duration, varying from simple "cold" treatments to severe "bronchial cold" in September, 1935, and hospitalization with German measles in April, 1936.

There followed one partially successful year of combined nose and throat treatment, supervised by the Medical Out-Patient Department, but with, as yet, no attention to the allergy. In addition to diet, sunshine, rest, and similar means of improving physical condition, plus instruction in avoidance of unnecessary contamination by the agents of infectious "colds," he was given a routine course of Cutter M.V.R.I. "shot" vaccine, going to 1.0 cc in nine injections at weekly intervals

between October 31 and December 17, 1938. The record of three "colds," one probably infectious, in December, 1938, and two probably allergic, one in April, 1939, with bronchitis and one in September with rhinitis, was definitely better than his average of previous years.

In September, 1939, an allergy history was taken and tests made. Positive tests were present to Kapok and to house dust. Treatment of the allergy was started with injections of a mixture made from the above substances. This was co-ordinated with the medical "cold" prevention regime to exclude infections and with local nose and throat treatment to assure drainage. There followed two years of complete freedom from "colds," i.e., September 30, 1939, to August 12, 1941, something he had never before experienced. The interval was long enough to indicate conclusively that combined treatment was apparently effective in the prevention of "colds."

Thus, it cannot be emphasized too strongly that the most important point for practical defense against "colds" in allergic individuals is to recognize that poor natural resistance to acute respiratory infections on the one hand, and allergic phenomena on the other, are two separate and entirely different entities, that both can produce the symptoms of "colds," and that uniformly successful treatment demands *adequate consideration and treatment of both.*

ALLERGY, POOR NATURAL RESISTANCE, HYPOTHYROIDISM

The many failures when patients were treated only by either the medical specialist, the nose and throat specialist, or the allergy specialist alone, without being given the benefit of essential care in other departments, serve well to illuminate the absolute necessity for co-operation, if a real and lasting success (no "colds" year in and year out) is to be realized. The following case history demonstrates how complicated the problem of preventing "colds" can be; i.e., even more than allergy and poor resistance to infections is involved, hence the necessity to combine medical, nose and throat, allergy, and any other treatment indicated by the individual problem, if any measure of success is to result.

Case No. 3—P. J. R., aged eighteen, had been subject to hay fever all her life, with a tendency to chronic sinusitis. She was classed as having poor natural resistance to infections because of her past illness: measles in childhood, mumps at six, chicken pox at eight, whooping cough at two, scarlet fever at seven, discharging ear at five, pneumonia at five and twenty-one, acute sinusitis at fourteen, and chronic sinusitis probably due to infection rather than allergy. Vaccinia showed a "take" at eighteen. In addition to hay fever "colds," she stated that she always had been subject to infectious "colds," averaging five each year. Tonsils and adenoids had been removed at five years of age, and, as the record shows, had not improved defense against infections.

General Physical Examination: Rather tall (68.8 inches) and slender (134 pounds) but essentially normal throughout. Blood pressure 106/60.

Specialists' Reports: Ear, Nose and Throat Department: tonsils absent; no adenoids.

1. August 25, 1938—nose normal, no obstruction, no polyps, no sinusitis.
2. March 4, 1941 (after pan-sinusitis and pneumonia)—nose clear, anteriorly and posteriorly.
3. December 2, 1941 (after a "cold" in nose)—"excellent condition."
4. February 10, 1942 (during acute sinusitis)—yellow-green nasal discharge, pain

over left eye, both maxillary sinuses moderately dark to transillumination, few greenish shreds on the left.

5. February 17, 1942 (after being in hospital with acute sinusitis)—transillumination all clear, small amount of pus in posterior ethmoids.

Laboratory Tests: Tuberculin P.P.D. (1) Negative. (2) Negative. Kline negative.

B.M.R. (1) 12-1-39 —11 Pulse 62 Wt. 140½
(2) 3-3-42 — 4 Pulse 64 Wt. 144
(Weight 130 lbs when taking thyroid extract)

Sedimentation rate (1) 3-10-41 8 mm
(2) 2-27-41 21 to 25 mm
(3) 3-5-41 20 mm

X-Ray Reports: Chest: February 19, 1941. No evidence of tuberculosis, mild root node calcification, heart and aorta within normal limits.

February 26, 1941. Small patch, probably bronchial pneumonia, at right base.

March 4, 1941. No evidence of tuberculosis. The small patch of bronchial pneumonia at the right base is no longer seen. Bronchial markings heavy.

Sinuses: February 25, 1941. Probably low-grade infection involving all the sinuses, but especially the antra, where there seems to be thickening of the lining membrane and possibly also a collection of fluid.

Treatment and Observations: During her first college year, August, 1938, to August, 1939, she did well because she continued to follow a regime set up by her medical, nose and throat, and allergy physicians outside the University. The record shows only one "cold," on September 13, 1938.

Again, in her second college year, August, 1939, to August, 1940, she did well, though not quite as well as the previous year, apparently due to omitting part of her program (the allergy treatment). This year she was managed by our staff, but with only the Medical and Nose and Throat Departments participating. The record shows a "cold" treated in Ear, Nose and Throat Department on September 1, 1939. She was then referred to the Medical Out-Patient Department for supervised "cold" prevention regime, with attention to rest, diet, sunshine, avoiding unnecessary contamination, et cetera. Lilly U.B.A. vaccine injections were given, nine in all, at weekly intervals from November 25 to December 21, 1939, and again between January 25 and March 5, 1940. The dosage varied from 0.1 cc to 1.0 cc. In addition to the vaccine, hygienic measures, and avoidance of contamination, she was given thyroid extract, with which the weight dropped from 140 to 130 pounds. She reported only two slight "colds." Since the allergy factors were ignored, the opportunity for a perfect result was probably lost.

The last two college years, 1940-1942, are a record of bad to worse, as the impetus of university demands for good marks and involvement in campus social life broke down her defenses against "colds." Chronic fatigue with acute fatigue superimposed at examination time, sleep average reduced to seven hours or less, no time for being outdoors in fresh air or sunshine, little exercise, and no attention to complete diet of fresh foods all had their effect. Likewise, no attention was given to avoiding exposure to infection at social events. The thyroid extract was discontinued and her weight increased to 144 pounds. Lilly U.B.A. vaccine was started again in October, 1940, but only five injections were taken, reaching 0.3 cc only of the vaccine (in our experience there is no real value to defense until dosage of 0.7 cc or over is reached). The record speaks for itself. She had influenza in December, 1940, acute pan-sinusitis and bronchial pneumonia which placed her in the hospital from February 23 to March 6, 1941, and again in April because of a respiratory infection. During these college years she was under the sole care of the Ear, Nose and Throat Department, being sent to the medical service in the hospital for treatment of the acute illness, if sufficiently prostrating, but with no attempt to influence the poor natural resistance to infections by a regime to improve her general

condition. Some oral "cold" capsules were ordered in March, 1941, by the Ear, Nose and Throat Department, but apparently were not taken, because she was forced by the repeated illnesses to drop out of college for the remainder of the term. The "cold" prevention regime of the Medical Out-Patient Department and the allergy were completely ignored.

The poor record continued during most of her last year at the University, August, 1941 to June, 1942. This second year of ignoring all aids to defense excepting hospital care, only during "colds" and their complications, shows: (1) December 1, 1941, "cold" treatment for a respiratory infection, (2) January, 1942, acute sinusitis, and (3) February 9, 1942, another much more severe attack of acute sinusitis which required hospitalization from February 10 to 14, 1942. Following this, she was finally referred back to the Medical Out-Patient Department for review and for setting up a co-ordinated defense to prevent "colds" and their complications, rather than to treat them after they occurred. For the first time the allergy history was obtained as well as the details of previous nose and throat and medical treatment—a saga of unsuccessful results when under each specialist alone. Her history just previous to entry to the University of California showed a prolonged period of excellent health with no "colds" when under the combined care of an internist, a nose and throat specialist, and an allergist.

Taking our cue from the success of the co-ordinated medical, nose and throat, and allergy treatment, the preventive regime was re-established by means of conscious effort to improve physical condition (normal rest, daily hours outdoors in pure air and sunlight, diet as complete and fresh as possible in a city), conscious effort to avoid unnecessary exposure to infection, thyroid extract, bacterial "cold" vaccines and later virus vaccine, control of the allergy by means of injections and diet, and local treatment of the nose and sinuses to assure draining. The beneficial effect was evident in the few remaining months at the University, i.e., no more "colds." She returned to the care of her home physicians for continued supervision, proving the worth of co-ordinated care in patients with both allergy and poor resistance to infections.

ALLERGY TREATMENT IN COLD PREVENTION

Case 4.—J. V. N. W., aged twenty years, always had been subject to infectious "colds" and since development of hay fever at fourteen years, and asthma later, had had almost constant trouble between infection and allergy.

She was classified as having poor natural resistance to infections because of a history of malaria at four, measles at six, chicken pox at six, whooping cough at six, tonsillitis at fourteen, influenza at sixteen, pneumonia at seventeen, vaccinia a "take" at three and at twenty years of age.

General Physical Examination: Normal throughout, medium development.

Specialists' Reports: Ear, Nose and Throat Department: August, 1941, the nose normal, no sinusitis, no adenoids, tonsils classed as "pathological," i.e., "city tonsils" at work. In October, 1941, during a "cold" with hay fever, the nasal membrane "appeared like hay fever." March 3, 1942, during asthma: nose clear, space good, tonsils slightly enlarged, granular pharyngitis, nasopharynx clear, larynx normal, no evidence of allergy in the head.

Allergy Reports: Dr. Albert Rowe and department, March 5, obtained a history that the hay fever began in 1935, with wheezing intermittent at first. Cold, foggy weather caused the worst asthma, i.e., as when sleeping on a porch in Berkeley; dust aggravated and the nose itched if Angora cat was near. However, skin tests were all negative, i.e., seventy foods, twenty-two emanations and dust, thirty pollens. No tests were made for sensitization to bacteria, even though the history showed frequent infectious "colds" for the fourteen years preceding development of hay fever and asthma.

Laboratory Tests: Tuberculin P.P.D. No. 1 negative. Kline negative. Urine normal. Hemoglobin 14.0 grams.

X-rays: Chest fluorogram—lungs normal. Calcified perihilar nodes.

Family History: Father subject to summer hay fever and asthma.

Treatment and Results: The first year and a half at college she had treatment only when "colds," hay fever or asthma occurred. Consequently, she ran her usual course of many "colds" and prolonged allergy reactions. The record is replete with treatments in the Ear, Nose and Throat Department for "pharyngitis," constant "cold" with sinusitis and headache, "allergic rhinitis," plus hospitalization for more severe "acute pharyngitis" and again for bronchial asthma.

The picture changes completely at the end of the second college year, i.e., spring of 1943. During the preceding spring she had been referred to Dr. Rowe and the Allergy Department by the Ear, Nose and Throat Department, and after history taking and skin testing (all negative as noted above) the allergy regime was added to the nose and throat treatments. Elimination diets were given a thorough trial without any benefit; aminophylline was given for control of the asthma but failed to influence the condition. Following referral for medical check-up and institution of a preventive regime for both the allergy and the susceptibility to infectious "colds" in the spring of 1943, she was given a 1:100 epinephrine spray, a course of mixed bacterial "cold" vaccine, and a hygienic regime. The asthma and hay fever were immediately controlled, defense against infectious "colds" improved greatly, and she did very well during the spring, summer, and autumn of 1943.

SUMMARY

The following conclusions are drawn from the study of the relation of allergy to "susceptibility" to "colds" in 2,380 University of California students and personnel:

1. Allergy is a separate entity from poor natural resistance to acute respiratory infections, must be recognized when present, and for good results must have treatment along with other therapeutic measures aimed at improving the "susceptible's" defense against "colds."

2. Since susceptibility to "colds" rarely has a single cause, being affected by some combination of the many factors which depress defense, it is imperative for each patient to have a history, complete physical examination, laboratory tests, x-rays, and specialists' opinions, before starting treatment.

3. Because multiple factors almost always influence the patient's defense against "colds" and no two cases are ever alike, best results are obtained from co-operative treatment by a group of conservative medical, nose and throat, and allergy specialists, with any additional care by others (dental, lung, specialists) if indicated.

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Room 126, Cowell Memorial Hospital

PERORAL PROPHYLAXIS OF POISON IVY DERMATITIS

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AMONG the many contact dermatitis to which man is heir, dermatitis venenata caused by poison ivy *(Rhus toxicodendron),* is probably the most common. It is so widespread in the United States that some investigators have considered the mechanism to be one of toxicity rather than allergy. Yet, many persons are immune to this offender. The oleoresin produced by the plant is believed to be the specific irritant or antigen which elicits the symptoms and signs of the disease in the susceptible individual. Straus[4] claims that the allergenic principles of poison oak, poison sumac and poison ivy are identical. Evidence to this effect was presented by Black, Coca and Shelmire.[2]

Efforts at prophylaxis against the effects of poison ivy were reported as early as 1829, when Dakin spoke of the "beneficial effects of chewing the leaves of the poison ivy plant" adding that it was an old practice among the American Indians. Schamberg recommended the use of Tincture of *Rhus toxicodendron* by mouth in increasing doses. Others (Strickler,[5,6] Williams, MacGregor, Fordyce et al) recommended desensitization by a series of injections of *Rhus toxicodendron* in oil. More recently dilutions of alcoholic solutions of the oleoresin have been administered. Spain[3] and Cooke reported favorable results from injections of these extracts. According to Biederman, desensitization to poison ivy also desensitizes to poison oak.

Tincture *Rhus toxicodendron* taken orally causes at times general pruritus, dermatitis, gastrointestinal disturbances, and pruritus ani. Shelmire,[2] who employed the oleoresin diluted in corn oil in daily, gradually increasing doses, advised interruption of treatment if erythema, urticaria, or gastrointestinal symptoms occurred. Special care is necessary in taking liquid oral preparations to avoid irritation of the lips or mouth.

Treatment or desensitization by injection is often painful, and repeated injections are often objectionable to the patient. The prophylactic results are varied: some investigators claim good results, others find no benefit from the injections.

Since E. Urbach[7] preferred oral desensitization whenever possible, and since he found the dry seeds to be uniform in potency while the leaves of the plants varied in their allergenic properties depending on the freshness of the leaves, he selected the dry seeds of the poison ivy as the antigen of choice. "Rhu-Sem" consists of ground dry seeds of the poison ivy plus

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"Rhu-Sem" was supplied by Dalare Associates, 2300 Locust Street, Philadelphia 3.
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glycyrrhizin to aid absorption and lactose to make enough bulk for handling.

The capsules are very small (size No. 5) and easy to swallow, even for a small child. There is no danger of contact irritation of the lips or the mouth.

This report is based on the prophylactic use of these capsules in 155 persons exposed to poison ivy at camp. Based on our previous experience with cases in the clinic and in private practice, the doses given the children were according to weight and age. Children between 45 and 75 pounds and approximately up to age nine were given capsules containing 1 mg of the ivy poison seeds. Those from 75 to 110 pounds and approximately between the ages of nine and thirteen were given 3 mg capsules, and those over 110 pounds and adults were given 5 mg capsules. The prescribed dose for all groups was one capsule daily a half hour before breakfast. All started taking the capsules about two weeks before going to camp, and all were instructed to continue taking one capsule every morning while at camp.

Children were accepted for this treatment only if they had a past medical history of ivy poison and showed a positive patch test with an acetone solution of the oleoresin of poison ivy, and a negative patch test[1] control.

In the summer of 1950, fifty-two were selected in the above manner and treated. There were forty-eight children and four adults. Nine girls in camp were free of dermatitis throughout the eight weeks of camp. Twenty-three boys went to an adjoining camp. None of the boys continued taking the capsules with any regularity after reaching camp, although they claimed taking them daily for two weeks before arriving at camp. Of these twenty-three boys, sixteen had no dermatitis during the eight weeks at camp. Four had very mild eruptions about the ankles lasting about three days. Three had eruptions, but much milder than in any previous year. In no case was it necessary to curtail their camp activities. Nine other boys went to another camp at scattered intervals of two weeks each, and were free of dermatitis while at camp. Four adults, two counsellors, and two caretakers of the grounds were also given prophylactic treatment. Three had no dermatitis; one of the caretakers had a very slight eruption about the wrists on two occasions during the summer. In previous summers this man had suffered severe attacks of dermatitis venenata. The remaining seven were private cases who had an entirely uneventful summer. Five of these had taken the capsules the previous two summers with freedom from dermatitis.

One girl, age five, stopped taking the capsules while still at home. It was later reported that she was developing an eruption; however, we did not see the eruption. One girl stopped the capsules when she had cramps. These may have been reactions to the capsules. There was no suspicion of any side reactions in the other fifty children. This is a matter to be

carefully observed in the subsequent prophylactic treatment with Rhu-Sem.

Another group of 103 Boy Scouts were treated prior to their summer encampment in 1948. This was a preliminary attempt to evaluate the effectiveness of this preparation. These boys had been in this camp previously, which was known for its heavy growth of poison ivy. The Scout leaders co-operated in the trying of this prophylactic treatment. Rhu-Sem capsules were supplied to 103 boys who gave a history of having had dermatitits venenata in previous years. Various groups went at different times and stayed one or two weeks; it was not possible to follow the groups while at camp. A questionnaire was sent to the parents after the summer vacation. Thirty-nine answered the questionnaire. With few exceptions the boys had taken the capsules from seven to seventeen days before going to camp. A few continued taking them at camp. Of this number twenty-one had no eruption at all, six had very mild eruptions, seven had some eruption but milder than in previous years. Three had the usual attacks. One of the three had poison ivy at home at the time he started the capsules.

One boy reported that while at camp he had diarrhea after the eighth capsule. He took no more capsules. He had no eruption. It is difficult to evaluate the reported symptom as a possible side effect in this case, as there were other children who had diarrhea while in camp without having had any treatment with these capsules.

We have also employed these capsules in the treatment of the acute stage of dermatitis venenata, but the number of cases is too small to report at this time. The patients in some instances felt that the severity of the eruption and the period of disability were less than in previous attacks. Caution should be exercised in prescribing more than one capsule daily in the treatment.

The duration of hyposensitization or desensitization in these children has not been determined. We have not pursued the treatment for prolonged periods of time, except in a few private cases, nor have we had sufficient experience with perennial treatment with Rhu-Sem. We have been impressed with the ease of administration and the freedom from untoward effects, except in a couple of questionable instances.

In summary, two groups are presented in whom desensitization to dermatitis venenata has been undertaken by the oral administration of dried seeds of *Rhus toxicodendron*. The results are very encouraging, the administration is simple, and the untoward side effects were very infrequent and extremely mild in nature.

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(Continued on Page 200)

NEWER ANTIHISTAMINES

Effectiveness and Side Effects of Long-continued Use of Ambodryl

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ANTIHISTAMINIC drugs have been in widespread use in this country for approximately six years,[1,2] but to date no study of their long-term effects appears to have been reported.

It is the present purpose to emphasize that (1) antihistaminic drugs may be effectively used against the symptoms of allergic disease over long periods of time; (2) no chronic toxic effects have resulted from their continuous use for two and a half years or more; (3) antihistaminic drugs are protective and not curative agents; and (4) recovery from the allergic state may ensue from long-continued use of a sufficient dose of the antihistaminic agent. While we have used Benadryl (diphenhydramine) hydrochloride in a few subjects for more than three years and have had long experience with some of the other antihistaminic drugs, our major clinical study has been with Ambodryl (B-(4-bromobenzhydryloxy) ethyl dimethylamine) hydrochloride because of its high therapeutic efficiency (twice that of Benadryl on a weight basis) and the low incidence of side effects (one ninth that of Benadryl).

SUBJECTS AND METHODS

Of 296 patients treated with Ambodryl for control of allergic manifestations,[4] forty-one have *continuously* received the drug in some dose for one year or more. During treatment, urinalysis, blood counts, and hepatic function tests have been performed once or more in each subject. Liver function has been tested by the single specimen procedure previously described,[5] which includes the determination of the icteric index, van den Bergh reaction, cephalin flocculation, thymol turbidity, alkaline phosphatase, serum proteins, albumin/globulin ratio, cholesterol, cholesterol esters, and, in some instances, the prothrombin time.

These forty-one patients have been seen on the wards and in the clinics of the Metropolitan Hospital and in private practice. The routine of management has been that of daily medical practice with care to avoid suggestive questioning either as to clinical progress or side effects.

These long-term observations have been made possible by the fact that Ambodryl completely or in major degree controlled the allergic manifestations, and attempts to decrease materially or to stop the drug have been followed by a return of symptoms. In some instances, in reducing the dose, a placebo has been substituted in such a manner that the number of

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TABLE I. DATA ON FORTY-ONE PATIENTS WHO RECEIVED AMBODRYL CONTINUOUSLY FOR TWELVE MONTHS OR MORE

Diagnosis	Total No. Patients	Treatment			Condition After Cessation of Therapy			Toxic Effects
		Duration (months)	No. Patients	Daily Dose† (mg.)	No. Stopped	Recovery		
						Complete	Partial	
Perennial Hay Fever	16	12	6	200 (1) 100 (4) 75 (1)	6	4	2	Drowsiness 2
		13	4	200 (2) 100 (1) 75 (1)				
		14	1	200				
		15	1	100				
		17	2	200 (1) 100 (1)				
		21	1	200 and 100				
		22	1	100				
Bronchial Asthma	15	12	4	200	6	3	3	Drowsiness 1
		13	4	200 (3) 200 and 300 (1)				
		14	2	200				
		16	1	200 and 300				
		17	1	300 and 200				
		22	1	300 and 200				
		24	2					
Atopic Eczema	6	12	1	300 and 200	4	3	1	Drowsiness 1
		14	1	200				
		17	1	300, 200 and 100				
		18	1	200 and 100				
		26	1	300, 200 and 100				
		29	1	200				
Gastro-intestinal Allergy	1	12	1	200	1	0	1	
Essential Hyper-tension	3	12	1	200	0	—	—	
		18	1	200				
		31	1	300 and 200				

†In this column is recorded the dose which the patient received for a major portion or all of the period of observation. The numbers in parentheses represent the number of patients treated at that dosage level. When more than one dose appears in the same line, it means that such a patient or patients successively received the drug for considerable periods of time at each of the indicated levels of dosage.

units of medication was not changed, so that any psychic influence might be minimized.

RESULTS

The results of the study are summarized in Table I. Partial or complete relief of all allergic manifestations was afforded each subject with the doses of drug used; otherwise the patient probably would not have continued the medication. Relief attained was complete in thirty-two patients and partial in nine. The only unpleasant side effect was drowsiness, complained of by four subjects, but not of sufficient magnitude to interfere materially with work nor to require discontinuance of the medication.

Of the sixteen patients grouped under the heading *sinusitis and perennial hay fever,* eight had readily demonstrable evidence of sinus infection, which even before the institution of other therapy showed some improvement as a result of antihistaminic medication. One of these subjects had been operated on for nasal polyps no less than six times and required one such operation during the year of treatment with the antihistaminic drug.

However, his nasal congestion was relieved even in the presence of the polyps which were causing nearly complete obstruction when Ambodryl was started. Two months later the polyps were removed. Nasal obstruction from this cause has not returned, and there is very little evidence of regeneration of the polypoid tissue, despite the fact that his previous operations had been followed by not more than two to three months of complete relief. Appropriate local nasal care was added to the regime in the other seven subjects with sinusitis as soon as symptoms had been maximally relieved by Ambodryl. As a rule, such therapy was begun within two to four weeks after the antihistamine had been started. In this group of cases it was rarely necessary to exceed a daily dose of 200 mg of Ambodryl to obtain optimal effects, and in only two subjects was a larger dose tried. These were the ones who had obtained partial relief only at the 200 mg level of dosage. Inasmuch as a trial for two weeks with 300 mg per day failed further to improve these subjects, the previous dose was resumed and maintained throughout the remainder of the period of observation.

Of the fifteen patients with *asthma,* a satisfactory prophylaxis against attacks was obtained in twelve by the use of Ambodryl alone. In the other three, Ambodryl in daily doses of 300 mg, while causing striking improvement, did not completely prevent the occurrence of early morning attacks. In these, the addition of Benadryl, 100 mg at bedtime, and a reduction in the amount of Ambodryl to 150 mg daily in three divided doses afforded further relief. However, in all three it was often necessary to employ a second similar dose of Benadryl when the patient awakened in the early morning with the slightest signs of an attack. The remaining twelve patients have been completely free of attacks when using proper doses of the drug (commonly 200 mg daily); as a rule, it takes one month of treatment to gain complete control of attacks. Five of these twelve patients have been able to stop the drug after twelve, twelve, twelve, fourteen and twenty-four months, respectively, without any return of asthmatic attacks in two, eight, fourteen, seven, and four months, respectively. Of these five patients, two were initially seen in status asthmaticus and four had had attacks of asthma for not less than four years, while onset in the remaining one was noted three weeks prior to the initiation of therapy.

Five of the remaining eight patients with asthma were first seen when in status asthmaticus. Of these eight, five have been kept free of attacks by the use of Ambodryl alone, and these include three of the subjects who were first observed in status asthmaticus. In three subjects, it was necessary to add Benadryl to the regime as above outlined. The average protective dose in asthmatic subjects has been 200 mg daily, divided into four equal doses spaced as evenly as possible throughout the waking hours of the patient. The longest period of continuous treatment of asthma has been twenty-four months, and the shortest eight months.

Of six subjects with *atopic eczema,* five have been completely controlled

with initial daily doses of 200 or 300 mg of Ambodryl. One was moderately relieved while taking 200 mg daily and has obtained still further decrease in itching and severity of the dermic lesions while using 300 mg per day. We believe that the lack of toxicity of Ambodryl is unusually well illustrated in one of these subjects, a boy of six and one half years at the time treatment was started, for whom 300 mg of drug daily proved necessary before the complete disappearance of his widespread skin lesions. This boy had a clinical allergy to eggs, wheat, milk, and chocolate, the introduction of any one of which into the diet would promptly cause a generalized pruritus, followed at first by a dry, erythematous eruption over most of the body and extremities, worse in all skin folds, and shortly followed by areas of "weeping." For twelve months this patient was given 300 mg daily of Ambodryl in four equal doses of 75 mg each. On this dose, it was possible to introduce gradually into the diet wheat, eggs, and milk without any return of symptoms. No attempt was made to add chocolate, as it was deemed nonessential to a normal routine of living. However, during this twelve-month period, it was not possible to reduce the dose of drug without a return of some of the skin lesions. From the twelfth to the eighteenth month of treatment 200 mg daily were necessary to prevent the appearance of skin manifestations, and for six additional months 100 mg daily were used. At the end of this twenty-four months' period of treatment, all therapy was discontinued while the patient was permitted a normal diet, exclusive of chocolate. During the six months which have since elapsed there has been no return of the skin manifestations. It is fully realized that the tendency for spontaneous recovery from these early childhood allergies is the rule rather than the exception. It is equally clear that Ambrodryl materially aided this patient, for up until the twenty-first month of treatment all medication could not be stopped without a recrudescence of the allergic syndrome. More important is the fact that the drug was well tolerated in the highest therapeutic doses without any sign of side effects, intolerance, habituation, bodily dysfunction, or organic change.

In atopic eczema it was generally possible to control the symptoms even though contact with the offending atopen could not be entirely avoided. One subject, a thirty-three-year-old single woman, a laboratory technician with sensitivity to formalin, has taken 200 mg daily for twenty-nine months, and has remained free of dermic lesions. Any attempt to diminish the dose has been followed by the appearance of urticarial or eczematous lesions, starting around the eyes and over the hands.

One patient with allergic manifestations in the mucous membranes of the gastrointestinal tract has been completely controlled by Ambodryl, which she has used continuously for twelve months in daily doses of 200 mg. We have not been able to find the cause of her disturbances, which include recurrent fever blisters, unusual dryness of the mouth, crampy abdominal pains, and occasional bouts of diarrhea. For the first time in

ten years she has been free of these while taking 200 mg daily of the antihistamine over a twelve months' period of time.

We were initially led to employ Benadryl in hypertension because of its frequently observed sedative action and its effect upon capillary permeability.[4] Some of the results were pleasantly surprising, although in many of the patients no reduction in blood pressure was attained. Because of this experience, Ambodryl has also been tried in hypertension; three subjects have used the drug for one year or more (Table I). In none of these has the blood pressure been materially affected, but all three state that they feel better while employing Ambodryl than without it. For this reason it has been continued, and one subject has taken it for a total of thirty-one months, at first in doses of 300 mg daily (for one year) and subsequently at the rate of 200 mg per day.

For at least three months ten of the forty-one patients have been *off Ambodryl therapy* without any return of allergic manifestions (Table I).

The absence of any symptoms or physical signs of a truly *toxic nature* from large doses of Ambodryl (up to 300 mg daily and total periods of treatment up to thirty-one months) emphasizes the relative harmlessness of the drug. In order to check this point further, all of these patients had one or more urinalyses and complete blood counts at the beginning of and during the period of therapy. Twenty-three of the forty-one were subjected to the single specimen test for liver function[5] (See also "Subjects and Methods"). In none of the results of the tests mentioned was there any evidence of a pathologic variant not already present prior to the initiation of therapy.

COMMENT

The present report deals with a specifically selected group of individuals with an allergy or hypertension who have continuously received Ambodryl, an antihistamine, for one year or more in daily doses ranging from 75 to 300 mg. The report has a threefold purpose: (1) to show that large doses of this antihistamine can be used over long periods of time without any harmful effects, (2) to emphasize the prophylactic rather than the "curative" value of the antihistaminic drugs, and (3) to suggest that the long-continued use of a potent antihistaminic drug may enable the patient to recover from a clinical allergy. By virtue of the method of selection, many allergic subjects have been eliminated from the present observations: those patients who required intermittent treatment, as for instance those with pollen hay fever; those with acute allergic conditions; those whose allergy was relieved by a short period of treatment and did not return after cessation of therapy; those for whom an antihistamine did not afford sufficient relief to justify prolonged administration; and those who developed a side effect of sufficient severity to warrant no further trial.

The present study indicates that relatively large amounts of the potent antihistamine drug, Ambodryl, can be employed for long periods of time

without fear of a chronic intoxication. Five patients have used the drug continuously for two or more years; six for from eighteen to twenty-four months; and thirty for from twelve to eighteen months. In view of the nature of the drug, we are of the opinion that any and all types of toxicity should have been uncovered in this time. Thus far all side effects have occurred within the first few days of treatment and include sleepiness (the only one ever present in any subjects of the present group), dizziness, and mild gastrointestinal upsets. Those who fail to show these early manifestations do not appear to develop any untoward effects even with the longest periods of administration.

The tendency for allergic manifestations to recur in these chronically sick individuals on cessation of or reduction in antihistaminic therapy suggests the prophylactic rather than the curative nature of this class of agents. It is equally clear that this prophylaxis can be carried forward for long, probably indefinite, periods of time, without harm to the patient and with continuously maintained relief from the clinical allergic picture. Inasmuch as all of the subjects studied had chronic allergies of long standing without effective relief by the use of other than antihistaminic agents, it appears that the prophylactic action of the antihistaminic drug may eventually lead to recovery on the part of the patient. By this statement it is not intended to imply that the patient has lost his allergic constitutional diathesis but rather that the threshold of one of his hypersensitive responding systems may have been considerably lowered by the prolonged suppression of histamine activity as a result of continuous drug administration.

The subjective relief afforded some patients with hypertension has as yet no satisfactory explanation. It is doubtful that it can be attributed *per se* to sedative action, although that is possible. There seems to be little influence upon the underlying condition, at least if one may judge from the failure of the drug to lower blood pressure. However, it is clear that relief has been sufficiently marked in these three patients for them to request the continued use of the preparation.

SUMMARY AND CONCLUSIONS

1. Forty-one patients with an allergy or hypertension have received Ambodryl in daily doses ranging from 75 to 300 mg for periods of time ranging from twelve to thirty-one months.

2. The allergic condition has been completely controlled in thirty-two of thirty-eight patients, and the remainder have shown major improvement. The three patients with hypertension have all reported subjective improvement from the use of the drug.

3. Ten of the thirty-eight allergic subjects have been able to stop the antihistamine after prolonged treatment without any subsequent return of symptoms.

4. Drowsiness, the only side effect observed, appeared early in the

treatment in four subjects but did not necessitate discontinuance of the drug.

5. It is concluded that Ambodryl is a highly effective, relatively nontoxic antihistamine which may be employed for prolonged periods of time without losing its effectiveness.

6. It is suggested that "desensitization" of allergic responding systems may occur when Ambodryl is employed for relatively long periods of time.

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NEW HONORARY MEMBER

The officers of the College take pleasure in announcing the election of Dr. Bernard N. Halpern, 197 Boulevard Street, Germaine VII^{E}, Paris, France, an Honorary Fellow of the College on February 15. Doctor Halpern's positions are as follows: Director of Research, National Center for Scientific Research; Chief of Laboratory, Faculty of Medicine, Paris; Professor of Allergy, Medical Clinic, University of Paris; Secretary-general of the International Association of Allergology; Fellow of the Academy of Sciences (Institute of France); Fellow of the Academy of Medicine of Paris; former president and now secretary of the French Society of Allergy. He has published numerous articles on medicine, physiology, and experimental and clinical allergy.

Doctor Halpern will be very active in the celebration of the fiftieth anniversary of the discovery of anaphylaxis which will be held on May 10 in the Sorbonne. Among those who have been made membre d'honneur of the committee of organization are Sir Henry Dale and Dr. C. Heymaus (Nobel Prize winners), and Drs. Cesare Frugoni, Arnold Rich, and Fred W. Wittich (president of the International Association of Allergology).

ABSORPTION OF AMINOPHYLLINE (THEOPHYLLINE ETHYLENEDIAMINE) FROM THE RECTUM

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THERE are relatively few drugs in which it is possible to determine blood levels, and this number becomes less when one attempts to define therapeutic blood levels. Recently we undertook a study on the administration of aminophylline to evaluate the dosage forms in which this drug is commonly prescribed.[6] The theophylline levels of the circulating blood were determined after the administration of various dosages of aminophylline by the oral, rectal, intravenous, and intramuscular routes. Time-curves of the appearance and disappearance of the drug in the blood stream were plotted, and the different levels attained were described. In view of the range of distribution of the values, we emphasized at that time the necessity of presenting such data in scatter diagrams. The greatest scattering of values occurred with the rectal suppositories and thus indicated pronounced individual differences in the absorption of aminophylline from the rectum. Some patients showed satisfactory absorption as reflected by high theophylline blood levels, while others had extremely low levels after this type of administration.

The rectal aminophylline suppository is used quite extensively in clinical medicine with satisfactory therapeutic results reported for many patients.[1,2,3,5] Our previous study was based on a single series of determinations on thirty-four individuals. In the present investigation we have re-evaluated this dosage form by using the same individuals but with multiple repeated determinations on each. The goal was to ascertain the constancy of results which can be expected in the same individual treated with aminophylline suppositories over a period of time.

MATERIALS AND METHODS

The patients used in this study were inmates of the San Quentin prison, all of whom had a previous diagnosis of bronchial asthma. The subjects were kept in bed throughout the entire seven hours of the test. In preparation for the determinations all medications were withheld for at least twelve hours prior to and during the time of the test. The patients received no breakfast that morning, and subsequent meals omitted caffeine-containing food or drink. The routine procedure consisted of obtaining a preliminary blood sample for blank estimation followed by administration of the aminophylline preparation. Subsequent blood samples were drawn

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at the first, third, and seventh hours, and were analyzed for their theophylline content by the ultraviolet spectophotometric method of Schack and Waxler.[4] The aminophylline suppository (Searle) used in this study contains 0.5 grams of theophylline ethylenediamine in a carbowax base. Although aminophylline was the drug employed, the determinations measured only the theophylline level of the preparation. This procedure was repeated at weekly intervals, so that some patients were tested as many as fourteen times and none had less than three separate determinations.

TABLE I. BLOOD THEOPHYLLINE LEVELS (MICROGRAMS PER 100 CC) FOLLOWING ADMINISTRATION OF .5 GRAM AMINOPHYLLINE SUPPOSITORY

	Patient	No. of Trials	1 Hour	3 Hours	7 Hours
Group I	Pen	14	93	193	133
	Dat	9	123	287	112
	Tay	8	56	236	212
	Jon	5	60	190	151
	Par	4	20	268	236
	Average	40	81	236	155
Group II	Cla	14	45	277	464
	Man	6	188	326	171
	Kir	6	57	257	325
	Gri	3	159	415	367
	Fis	3	228	472	441
	Tab	3	194	460	612
	Dig	3	0	286	302
	Average	38	103	324	400

RESULTS

Table I indicates that only five of the twelve patients had average values of over 100 micrograms of theophylline per 100 cc of blood one hour after administration of the suppository. By the third hour, however, all patients showed values above this level. These levels were maintained or elevated in most of the patients through the next seven hours.

It is apparent from the table that there are two types of individuals as determined by their absorption of aminophylline from the rectum. Group I does not achieve an average of more than 300 micrograms of theophylline in any of the blood samples taken during the seven-hour period. Group II has consistently good absorption from the rectum, with individual values of 500 to 600 micrograms of theophylline and a group average of 103, 324 and 400 micrograms over the course of the seven hours.

The data obtained from one subject in each group [Pen (Group I) and Cla (Group II)] is presented in a scatter diagram to indicate the range of distribution. Both patients had been treated fourteen times with aminophylline suppositories. These patients showed no significant difference in theophylline levels at the first hour. However, subsequent samples at the third and seventh hours show marked differences in the absorption from the rectum as reflected by theophylline blood levels.

DISCUSSION

The following considerations are involved in absorption from the rectum: (1) drug solubility, (2) retention of the suppository, (3) type of

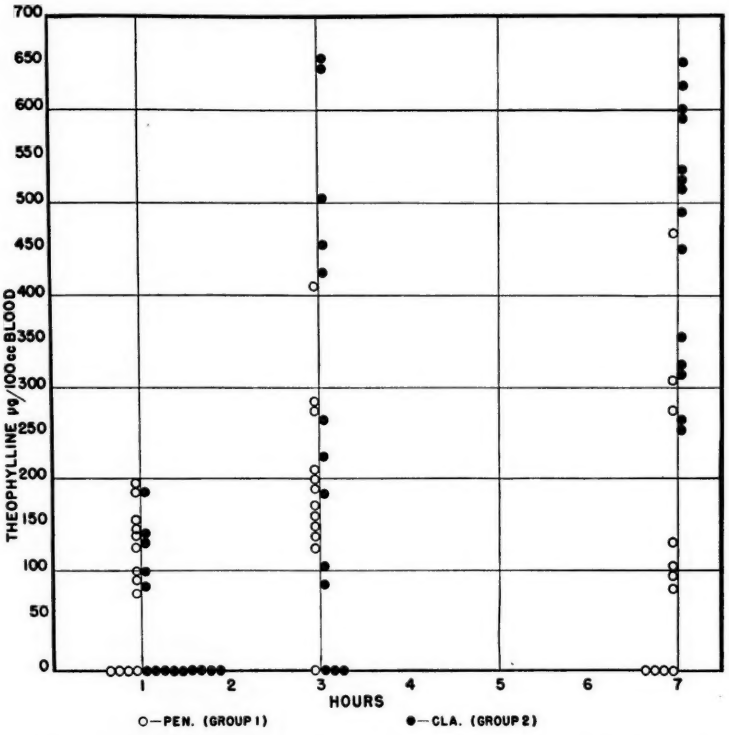

Fig. 1. Blood theophylline levels after administration of aminophylline rectal suppositories; patients treated fourteen times at weekly intervals.

vehicle used, (4) status of the rectum as regards the fecal contents, and (5) the type of individual.

It is apparent that the degree of absorption of the medication from the rectum is quite variable. Most individuals tested show only fair or minimal absorption within the first hour, but by the third hour all patients show levels above 100 micrograms per cent and these tend to go even higher at the seventh hour. In about one half of the patients the concentration never exceeded 300 micrograms per cent, while in the other half much better absorption was consistently observed. It thus appears that the rectal suppository may be of value particularly to those people who show good absorption of this drug from the rectum. In this group of patients the levels which occur once the absorption begins are of such magnitude as to make them therapeutically effective if we can assume that there is some correlation between high theophylline levels and therapy. Since significant levels are reached over a seven-hour period and since in some cases these levels are quite high at the end of this period, it is a rational and reasonable

dosage route for use in those patients requiring effective therapy over this period of time, particularly during the night hours.

CONCLUSIONS

1. Theophylline blood levels were determined following repeated administration of aminophylline rectal suppositories to patients.

2. There were two groups of individuals as determined by the absorption of theophylline from the rectum. One group had good absorption as reflected by high theophylline blood levels, and the other group had correspondingly lower levels in all the blood samples tested.

3. In the first hour, appearance of the drug in the blood stream was minimal, with low theophylline levels. All patients showed significant blood theophylline three hours after administration of the suppository.

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INTERNATIONAL CONFERENCE ON TUBERCULOSIS

The Twelfth Annual Conference of the International Union Against Tuberculosis will be held in Rio de Janeiro, Brazil, August 24 to 27. Dr. J. Burns Amberson, visiting physician in charge of the chest service will present the principal report: "Treatment and Prognosis in Minimal Pulmonary Tuberculosis."

Other papers will be on "Immunity and Tuberculosis," with Prof. Arvid Wallgren of Sweden as the principal speaker, and "Organization and Results in Regard to the Tuberculosis Campaign of Mass Surveys," with Dr. Fernando Gomez of Uruguay as the chief reporter. Discussors of the various papers have not yet been designated.

Prof. Manoel de Abreu of Rio de Janeiro, president of the Union, will preside at the conference.

LOBELINE IN THE TREATMENT OF ALLERGIC DISORDERS

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LOBELINE is one of the alkaloids obtained from *Lobelia inflata*, but commercial preparations generally consist of the sulfate or hydrochloride of pure, stabilized alpha-lobeline. Since the plant grows so abundantly in southern Chile[4] and since there have been some published reports defining its use in certain types of allergic dermatoses, we believed it worthwhile to investigate clinically the therapeutic action of lobeline in a number of patients sufficiently large to permit drawing some conclusions concerning its indications and action.

The classical indications for lobeline are asphyxia neonatorum and respiratory failure due to intoxication or anesthetic accidents. According to older conceptions, lobeline excited the respiratory center directly. However, recent work by Haymans, Euler and others suggests that lobeline acts by way of the carotid sinus because, after extirpation of the carotid sinus in dogs, lobeline has no stimulating action upon respiration.

Quite by chance it was found that lobeline possesses therapeutic actions other than those already mentioned. In a case of asphyxiation due to Quincke's edema in the region of the glottis, lobeline was given to help restore respiration. Theoretically no beneficial effect could be expected because in this case failure was not due to paralysis of the respiratory center but merely to mechanical obstruction. Nevertheless, the asphyxiated condition improved and within a few hours the large urticarial wheals present also disappeared.

This casual observation prompted various investigators to employ lobeline in various other allergic manifestations. Thus Moser[5] in 1932 reported upon seven patients treated for urticaria with parenteral lobeline. Six of these obtained complete relief, with rapid recovery. It was not until eight years later, in 1940, that this fact was again observed. Throughout a diphtheria epidemic in Bulgaria during the winter of 1939-1940, Dimitroff[2] treated with lobeline all those individuals suffering from serum sickness due to the antidiphtheria injections each patient received. Dimitroff administered 10 mg of lobeline to adults and 3 mg to children. These doses were given twice daily subcutaneously. In general, three to four injections were necessary for each patient in order to completely erase symptoms. In the twenty-one cases treated with lobeline, an average of 1.8 days was required for successful treatment. According to North American workers,[1] an average of 5.4 days is needed for the treatment of serum sickness when medicaments other than lobeline are used. In 1941 another Bulgarian

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From the San Francisco de Borja Hospital, Section B Medicine (Prof. Dr. M. Hermosilla, Santiago).
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TABLE I

Diagnosis	No. of Cases	Immediate Relief			Lasting Relief		
		Complete	Incomplete	None	Complete	Incomplete	None
Urticaria	20	15	2	3	2	12	6
Urticaria caused by physical allergies (e.g., cold, heat, etc.)	12	2	6	4	1	5	6
Quincke's edema	10	2	6	2	2	3	5
Allergic dermatitis	17	6	10	1	6	7	4
Dermatitis caused by drugs	3	3	—	—	1	2	—
Weeping eczema	4	—	1	3	—	1	3
Neurodermatitis	3	—	3	—	—	2	1
Psoriasis	2	—	—	2	—	—	2
Infantile prurigo	2	2	—	—	1	1	—
Bronchial asthma	4	—	—	4	—	—	4
Allergic rhinitis	3	—	1	2	—	1	2
Total No. of Cases	80	30	29	21	13	34	33
Percentage	100%	37.5%	36.25%	26.25%	16.25%	42.5%	41.25%
Cases without respiratory allergy	73	30	28	15	13	33	27
Percentage	100%	41%	38.35%	20.65%	17.94%	45.2%	36.8%

physician[6] published his results after treating with lobeline seven patients suffering from weeping eczema. Within two to three days all patients displayed notable diminution of both exudate and itching.

In 1943 Franck[3] reported on forty-three cases of urticaria successfully treated with lobeline. He concluded his paper by saying: "It is practically impossible to imagine the way in which lobeline acts in these cases or why it has such good effects. For this reason we are limited simply to report the constancy of our observations."

Because of this publication and with a certain reservation due to the obscurity of its possible mechanism of action, we commenced our studies in 1945 by employing lobeline in various types of allergies.

TYPES OF PATIENTS AND METHODS OF THERAPY USED

From 1945 until June, 1951, we treated eighty patients, thirty-four of whom were hospital and forty-six private patients. Of these forty-four were men and thirty-six women. Their ages varied from five to sixty-three years, with an average of thirty-four years. We administered alpha-lobeline hydrochloride* to all patients subcutaneously two or three times daily according to the severity of the case. Lobeline must be given intravenously for all types of respiratory accidents, but this method was inefficacious in some of our patients and for this reason we decided to use subcutaneous injections exclusively. Children were given 3 mg ampules, whereas adults were given 10 mg ampules. In no case did we observe side reactions disagreeable to the patient. The total dose required for each patient was from 6 to 20 ampules, with an average of 8 ampules. The results obtained in the various clinical complaints are shown by Table I.

*This was kindly supplied to us by Sandoz, Ltd., Basle, Switzerland, as Lobeline-"Sandoz" in 3 mg and 10 mg ampules.

COMMENT

Analysis of this table shows that the great therapeutic success of lobeline in some allergic states provides a vivid contrast to the other allergies in which no improvement at all was obtained. The greatest effect was obtained in urticaria, where 75 per cent of the patients showed rapid improvement, i.e., the itching and general malaise ceased within a few hours and the wheals disappeared very rapidly. In febrile patients the temperature was lowered without the use of antipyretics. In contrast, the cutaneous manifestations of physical allergies did not respond well, and only 16.6 per cent of patients showed an immediate and complete improvement. It may be argued here that urticaria is a condition having irregular phases and that urticarial manifestations subside spontaneously or suddenly appear at any time without warning, thus making evaluation of the results of any specific treatment almost impossible. This is true. Nevertheless, the fact that 75 per cent of our patients were previously treated without success and then obtained rapid, complete, and even spectacular cures with lobeline is of important clinical and statistical significance. This cannot be denied.

Up to now no other treatment has been able to equal this success. Cortisone and ACTH may produce a favorable therapeutic effect in the majority of cases—but application of these hormones should be reserved for other indications, and there is no justification for their use in some allergic conditions when lobeline makes treatment so simple, rapid, efficacious, economical, and free of all side effects.

RELATIONSHIP TO OTHER THERAPY

Eighty per cent of our patients had previously received other methods of treatment without results.

Antihistamines.—Because of the fact that antihistamines have been available in our country for only two years and that our report includes numerous observations made previous to their advent, only 40 per cent of our patients received antihistaminic treatment previously. In these cases lobeline was given only after insufficient results were obtained with the antihistamines.

Specific Treatment.—Fifty per cent of our urticarial patients had an etiology of alimentary allergy as proved by auto-observation and blood, leukopenic, and diet tests. Nevertheless—and this has also been reported by various other authors—it was found that elimination of the causative factors did not always imply rapid improvement. Urticaria may persist for days and weeks after the last ingestion of an allergic foodstuff. Moreover, it may even appear many days afterwards by the trigger action of physical and psychic stress. Under such circumstances a medicament capable of producing rapid disappearance of the symptomatology is of great benefit because it gives the physician much more time to carry out basic

specific desensitization treatment. *However, lobeline given alone, even over long periods of time, does not maintain the patient free of symptoms* unless desensitization therapy is also carried out.

The results obtained with lobeline were very favorable in both allergic dermatitis and the special dermatitis caused by drugs. On the other hand, in bronchial asthma and allergic rhinitis the therapeutic results were very poor. This fact immediately attracted our full attention. Why does lobeline give such favorable response to cutaneous allergies and why does it give no response to respiratory allergies? No answer can be given to this question until we recognize its exact mechanism of action. Recent investigations pointing out the great importance of the interrelationship between the endocrine—hypothalamus-pituitary-adrenal cortex—systems in the pathogenesis of various hypersensitive states, lead us to believe that lobeline has an action directly upon the hypothalamic centers and causes secretion of ACTH. We are studying this possibility at present together with the question of the relationship of lobeline with various histamine levels. This work began only recently, and we can render no opinions at this time.

CONCLUSIONS

The therapeutic action of lobeline was studied in eighty patients suffering from various hypersensitive conditions.

Of twenty patients with urticaria, 75 per cent obtained rapid relief.

Very favorable results were obtained in twenty patients suffering from allergic dermatosis.

Lobeline had no specific therapeutic effect in bronchial asthma and allergic rhinitis.

Suggestion is made of the possibility of lobeline acting through the hypothalamus-pituitary-adrenal cortex system.

Lobeline gave rapid relief in allergic dermatosis, but this treatment had to be combined with desensitization therapy in order to assure prolonged or complete relief.

Lastly, we are of the opinion that lobeline will have great therapeutic possibilities in the future and that thus all efforts possible should be made to produce lobeline in Chile because we possess large areas of territory which are now "overrun" by *Lobelia inflata* plants.

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Catedral 1165

HYPOALLERGIC PENICILLIN

IV. Chlor-Trimeton-Penicillin

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Dayton, Ohio

CONTINUING our investigations with antihistaminic drugs as to their ability to suppress reactions to penicillin, the present study is concerned with Chlor-Trimeton® and its effects when it is added to injected penicillin.

In earlier papers[16,17,18] it was noted that the use of antihistaminic drugs is still empirical and that frequently it is necessary to vary the dosage and the interval between doses as well as the antihistaminic preparations in order to discover the best one for a particular condition or patient. It would appear that at least 1,000 patients must be treated with any antihistamine-penicillin mixture before definite conclusions as to the efficacy of the antihistaminic drug in preventing reactions can be determined. Controls, while of some value, would cause the studies to take twice the time (now about eight months) and are not really necessary, since the various series act as controls for each other.

The ideal preparation would be a penicillin or penicillin mixture with unaffected therapeutic efficiency which produced no reactions. Such has not as yet been attained. A new penicillin (Compenamine®) has been offered to the medical profession, and yet its rate of reaction, as reported,[9] is higher than those seen in a similar series of more patients in whom penicillin combined with an antihistaminic drug was used.[18]

Various studies have shown that neither the skin test nor the passive transfer reaction is a reliable index of penicillin sensitivity.[4,14] It would seem logical to use a penicillin mixture which has a proved low rate of reaction. Therefore, we plan to continue the study of various antihistaminic drugs mixed with penicillin until we find the ideal mixture or as close as possible to it.

METHOD

In the present study the Chlor-Trimeton-penicillin (hereafter referred to as CT-penicillin) was prepared by the following method:

Chlor-Trimeton was available as a 10 per cent solution in 10 ml ampules. Each ampule contained 1 gm of the drug in 10 ml of saline. The contents of one ampule dissolved in each 1,000 ml of sterile buffered saline produced a 0.1 per cent solution, while if two ampules were used for

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Sponsored by the VA and published with the approval of the chief medical director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Chlor-Trimeton (Chlorprophenpyridamine maleate) was supplied through the courtesy of the Schering Corporation, Bloomfield, New Jersey.

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1,000 ml, a 0.2 per cent solution was obtained. This was the diluent used for the crystalline potassium penicillin G (Squibb, Bristol or Schenley) which was standardized at 100,000 units per ml.

During the eight months of these studies, 1,096 patients received over seven billion units of CT-penicillin. The individual dose varied from 100,000 to 600,000 units given from one dose only to one dose every three, four, six, eight, twelve, or twenty-four hours. The lowest total dose given any one patient was 100,000 units, and the highest 35,900,000 units (over a period of twenty-six days). The maximum dose in each twenty-four hour period to one patient was 1,800,000 units. The average dose for all patients was 6,000,000+ units. The majority of the patients had previously received some form of penicillin.

As in the earlier series the antihistaminic drug was used in 0.5 and 1 per cent concentrations, there may be some question as to why so low a concentration was used for Chlor-Trimeton. It was felt that as the oral dose (4 mg) was approximately one tenth of the oral dose of Histadyl® (50 mg) which had been used as 1 per cent solution, 0.1 per cent would be sufficient. However, after four months of study the concentration of the antihistamine in the diluent was doubled, with definitely superior results. Six hundred twenty-six patients were treated with the 0.1 per cent solution and 470 with 0.2 per cent.

RESULTS

All reactions, local or generalized, which could be attributed to penicillin or any other drug were referred to the author, who personally studied each patient.

In the first four months of the study, using the 0.1 per cent diluent, there were twelve reactions, or 1.91 per cent. Rather than giving details of each case, salient points will be noted. Half of the total, or six patients, had also been given another antibiotic previous to the development of the reaction. Three had received streptomycin, two chloromycetin, and one aureomycin. Four, or one third, of the total had received penicillin previously. One patient had had more severe urticaria at an earlier time but no penicillin before the present course. In only one patient was it necessary to continue penicillin, and his treatment was immediately changed to an antihistamine-penicillin in oil (containing 22 mg of antihistamine per 300,000 units of penicillin in each ml). The urticaria began clearing after the first injection and after two days had entirely disappeared. One other patient developed a severe anaphylactoid type of reaction and immediate urticaria after the first injection. He had had penicillin several times previously and later produced a 3+ reaction within fifteen minutes to 40 units of penicillin given intracutaneously. It is believed that this was an accidental intravenous injection.

During the last four months, using the 0.2 per cent diluent, there were

but three reactions, or 0.64 per cent. The details of these three patients are presented briefly:

Case 1.—C. C., aged seventy-three. Diagnosis: coronary occlusion. The patient had also received Demerol, irradiated plasma, whole blood, heparin, atropine, Dicumerol, Mercuhydrin, and sodium luminal. Penicillin had not previously been given. CT-penicillin, 300,000 units, had been given daily for five days when there developed a generalized macular, nonpruritic eruption. An oral antihistaminic drug three times daily was administered, and the skin was completely clear in two days.

Case 2.—A. C., aged sixty-eight. Diagnosis: cardiac decompensation. The patient had also received digitoxin, multi-vitamins, and Thiomerin. There was no history of previous penicillin. CT-penicillin, 100,000 units every three hours, had been given for forty-eight hours when an urticarial eruption appeared on the legs and thighs. The penicillin was stopped, and with the administration of an oral antihistaminic drug every four hours the skin cleared completely in one day.

Case 3.—O. S., aged fifty-two. Diagnosis: (1) paroxysmal auricular flutter—congestive heart failure; (2) pneumonia, left lower lobe with possible pulmonary embolus or abscess; (3) rheumatoid arthritis; (4) cortisone intoxication. For fifteen months the patient had been taking cortisone (25 mg tablet three times daily) intermittently; when peripheral edema developed, he lowered the dosage. After about ten months a sudden onset of tachycardia was terminated with digitalis. Cortisone was finally stopped because of ankle edema and generalized pruritus. The next day, tachycardia accompanied by extreme dyspnea recurred. The following day, pleuritic and anterior chest pain was added. He entered the hospital and on the next five days received aminophylline, morphine, digitoxin, Mercuhydrin, codeine, aspirin, and CT-penicillin (150,000 units every three hours night and day). The penicillin was stopped on the fifth day because of the development of a generalized pruritic, punctate, confluent, red eruption. Hemorrhagic purpura appeared on both legs. The eruption cleared slowly without further medication. He had had penicillin previously.

All three of these cases are considered to be reactions to penicillin, although there is some question concerning the third patient.

As with the other antihistaminic drugs used, all the patients noted the local anesthetic effect of the Chlor-Trimeton. With as much as 6 ml given at one injection, there were no complaints of pain or residual tenderness. No side reactions, such as occur with oral antihistamines, were noted.

Therapeutic results were as good as with any other type of penicillin. Frequent blood counts, urinalyses, and other laboratory studies disclosed no adverse reactions due to the added Chlor-Trimeton.

DISCUSSION

The reaction rate, using 2 mg of Chlor-Trimeton per ml, compared favorably with the other antihistaminic drugs which have been tried. Because of its potency, smaller amounts of the drug were eminently satisfactory. It is possible that even higher concentration could cut the reaction rate further, and at the present time studies on this are being carried out.*

*In 750 patients with a total dose of four and a half billion units of penicillin, when Chlor-Trimeton was used in the diluent as 0.3 per cent (3 mg per ml), only three mild skin eruptions occurred. All cleared completely in two days with additional antihistaminic drugs. The reaction rate for this concentration is thus 0.4 per cent.

The higher percentage of reactions, using the 0.1 per cent diluent, was to be expected but possibly could have been reduced if other antibiotics, not covered by the small amount of antihistaminic drug, had not been given. Many patients received two or more antibiotics in each series without reaction. The literature reveals reactions to streptomycin,[5] aureomycin,[3] and Chloromycetin.[1,6] The optimum dose of the antihistamine lies somewhere below the toxic dose but above the dose necessary to suppress a reaction in the most penicillin-sensitive individual so that excess is present to prevent reactions from other sensitizing agents. This favors the use of a drug like Chlor-Trimeton where the effective dose is small and yet is far from being a toxic dose.[11] We must also consider the presence of refractoriness in a certain percentage of patients or its development after antihistamine therapy, which may account for some of the reactions.[12]

The author does not subscribe to adding antihistamines to procaine penicillin because it is felt that the procaine is not necessary and another sensitizing agent has been added.[8,10] Instead, our preference is for regular penicillin with the oil-soluble antihistamine base and 2 per cent aluminum monosterate in sesame oil which gives therapeutic levels for twenty-four hours, the longest period deemed safe should a reaction ensue.[17]

Reactions from penicillin are definitely increasing since it is being used so frequently without adequate indication, as in the common cold. The general reaction rate is now about 7 per cent of all patients treated with penicillin.[2]

Crossed sensitivity has been found to penicillin O,[15,20] and the reaction rates with Compenamine are higher in a smaller series[9] than in ours where an antihistaminic drug was used.

The question has been asked, "Why not give oral antihistamines with penicillin?" The answer is that these drugs may prove undependable orally,[7] and it has been shown that many times when the response was poor from oral administration, a better response was obtained by parenteral administration.[13,19]

SUMMARY AND CONCLUSIONS

Chlor-Trimeton, when added to the diluent for crystalline potassium penicillin G, definitely reduces the number of reactions. This reaction rate is lowered as the amount of the antihistaminic drug given is raised. The rate in 626 patients in which 0.1 per cent Chlor-Trimeton was used was 1.91 per cent, while in 470 patients in which a 0.2 per cent was used the rate was 0.64 per cent.

ACKNOWLEDGMENT

The author wishes to express his gratitude to Mrs. Lila Rinard and Miss Hazel Durkin for their invaluable assistance in the preparation of this paper.

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PHYSICIAN SEEKING POSTGRADUATE STUDIES IN ALLERGY

A physician practicing in South Africa writes that he is desirous of securing a position in an American hospital or institution where he may continue his postgraduate studies in allergy and at the same time earn a livable income. He is twenty-eight years old, married, and has two children. He qualified in England in 1948, and after his hospital appointments and Royal Air Force service, he went to South Africa and entered general practice.

He is mainly interested in allergy and carries out his allergy studies at the local hospital. He is very eager to continue his studies in allergy in the United States, and living conditions here would require that he have a supporting salary.

If any member of the College knows of a possible location or knows whether there is any established allergist who might need a keen assistant, he is urged to write this information to ANNALS OF ALLERGY, 401 LaSalle Medical Building, Minneapolis 2, Minnesota.

TREATMENT OF HAY FEVER BY AN INTRAVENOUS ANTIHISTAMINE

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VARYING degrees of success have been reported following the use of oral antihistaminic agents for the relief of hay fever and vasomotor rhinitis.[3,6] In addition, parenteral antihistamines have been used not only for the treatment of allergic disorders but also (as reported by Maietta[5]) for decreasing the number of pollen injections and increasing the amount of antigen in each desensitizing dose. Simon[8] reported similarly encouraging results from the use of an antihistaminic diluent for penicillin in patients sensitive to that antibiotic.

In this report the antihistamine* (Decapryn Succinate Minergic Solution) was given by intravenous injection to alleviate temporarily the symptoms of perennial vasomotor rhinitis and seasonal hay fever. At the same time hyposensitization with specific antigens by subcutaneous injections was carried out. Only cases relatively resistant to oral antihistamines because of severe nasal obstruction, much discharge, or sneezing were chosen. One hundred consecutive severe cases falling into the above category are herewith reported.

Eighty-two cases were perennial and the remaining eighteen were seasonal (ragweed, fall type). The patients varied from twelve to seventy-five years of age; 60 per cent were female. The results are tabulated as follows:

Excellent relief	66 cases
Good relief	22 cases
Fair relief	10 cases
No relief	2 cases

Those included in "excellent" obtained practically complete cessation of symptoms in a short time (from twenty minutes to one hour). Strangely enough, the relief usually lasted several days following a single injection in contradistinction to oral antihistamines which usually produce very temporary effects.[1,2,4,7] This relief was much greater than that usually obtained in ordinary treatment, especially early in the course of treatment. It is uncertain why this relief should last so long. Those classified as "good" obtained nearly complete relief for several hours up to one day. "Fair" relief included those with about one-half alleviation of symptoms. The perennial cases showed a slightly higher percentage of excellent relief, but the number of seasonal cases was small.

The reactions, if anything, were less than in oral administration of antihistamines.[3] Fifteen per cent reported a moderate amount of sleepiness.

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*Decapryn Minergic Solution contains 5 mg Decapryn Succinate per 1 cc. "Decapryn" and "Minergic" are trademarks of The Wm. S. Merrell Company, Cincinnati 15, Ohio, from whom supplies were obtained.

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No one was completely incapacitated. Sixteen per cent in addition were made slightly drowsy. One reported vertigo, one nervousness, and one headache. No other reactions were noted.

It was found most convenient to dilute the Decapryn Minergic Solution with equal parts of sterile water and inject it intravenously with the patient sitting up. The doses varied from 0.8 to 2.5 cc Decapryn Minergic Solution (4 to 12.5 mg of Decapryn), though the usual dose was 1.0 cc. No immediate reactions were noted in any case.

It is felt that such a regime as outlined increases the immediate relief obtained by the patient and makes him much more comfortable while awaiting the slower but perhaps surer relief from hyposensitization. It merely supplements standard treatment, producing more comfort earlier than frequently obtained heretofore in many cases.

SUMMARY AND CONCLUSIONS

A method is presented of supplementing the usual treatment of seasonal hay fever and perennial vasomotor rhinitis by intravenous injection of an antihistamine. The results obtained in a series of 100 cases treated with intravenous Decapryn Minergic Solution are superior to those obtained prior to its use.

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POSITION OPEN FOR ALLERGIST

The Scott and White Clinic, affiliated with Scott and White Memorial Hospitals and Scott, Sherwood and Brindley Foundation, Temple, Texas, is in need of a man capable of doing internal medicine and allergy. Please inquire directly of A. Ford Wolf, M.D., Scott and White Clinic, Temple, Texas.

THE INTRANASAL USE OF PROPHENPYRIDAMINE MALEATE AND CHLORPROPHENPYRIDAMINE MALEATE IN ALLERGIC RHINITIS

NATHAN SCHAFFER, M.D., F.A.C.A., East Orange, New Jersey
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THE antihistamine prophenpyridamine maleate (Trimeton-Schering)[4] in recommended doses has been reported to afford partial to complete relief in 60 to 85 per cent of patients with allergic rhinitis.[1,3] Chlorprophenpyridamine maleate (Chlor-Trimeton Maleate-Schering)[5] has been described as being 50 to 85 per cent effective in offering relief to patients similarly afflicted.[2,6,8,9]

It was the purpose of this study to observe the effects of these two antihistamines when applied intranasally to patients with allergic rhinitis. Prophenpyridamine maleate was made available in a concentration of 0.5 per cent in plain aqueous solution, and chlorprophenpyridamine maleate was available as a 0.25 per cent aqueous solution.* Pharmacologic studies had previously determined the preferability for the concentrations and the plain aqueous vehicle used.[7]

Selection of Patients.—The 144 patients in this study ranged in age from two to fifty-seven years, with the majority being in their third decade. All had had a positive diagnosis of allergic rhinitis. As this study was begun near the end of the 1950 ragweed season, ragweed pollen rhinitis patients comprised a portion of this group. The group of patients included those previously responding to antihistamines, those not responding to antihistamines, and some who had not received any previous antihistamine therapy. The patients in this study were divided into two groups. Eighty-three patients received the prophenpyridamine maleate solution 0.5 per cent, and sixty-one received the chlorprophenpyridamine maleate solution 0.25 per cent.

Dosage and Procedure.—Three drops of the solutions used were instilled into each nostril. Some patients were instructed to keep the head lowered between both knees for five minutes following the instillation. Others were instructed to instill the drops with the head extended over the edge of the bed while lying on the back. The instillation of the drops was to be repeated every four hours, if necessary, at home. No patients are included in this series who did not use the solutions for at least two weeks. The majority of patients continued the medication for two to three months, as needed, and a few have used the medication for nine months.

The first instillation of the solution into the nose was followed by direct observations of the nasal mucosa to determine the time of onset and degree

*The preparations used in this study were supplied through the courtesy of Schering Corporation, Bloomfield, New Jersey.

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TABLE I

Antihistamine Preparation	No. of Cases	No Relief	Fair Relief	Good to Excellent Relief	Total Response
Prophenpyridamine maleate solution 0.5%	83	10 (12.0%)	5 (6.0%)	68 (82.0%)	73 (88.0%)
Chlorprophenpyridamine maleate solution 0.25%	61	6 (9.8%)	7 (11.5%)	48 (78.7%)	55 (90.2%)

of vasoconstriction. In practically all instances where vasoconstrictor action was observed, the time of onset was from seconds to one minute. On subsequent office visits, the nasal mucosae were carefully observed, and the patients were carefully questioned concernng the degree and duration of nasal vasoconstriction experienced.

Evaluation of Results.—Table I summarizes the degree of vasoconstriction observed and subjectively reported in this study.

In the eighty-three patients receiving the prophenpyridamine maleate solution 0.5 per cent, ten (12.0 per cent) did not obtain any vasoconstrictor effects. Five patients (6.0 per cent) showed slight to moderate vasoconstrictor effects which lasted two hours or less. Sixty-eight patients (82.0 per cent) exhibited moderate to complete nasal vasoconstriction which lasted four to six hours or longer. Two patients claimed relief for twenty-four hours following the instillation of the drops.

In the sixty-one cases receiving chlorprophenpyridamine maleate solution 0.25 per cent, six (9.8 per cent) failed to obtain any benefits. Seven (11.5 per cent) obtained slight to moderate vasoconstriction lasting two hours or less. Forty-eight patients (78.8 per cent) exhibited moderate to complete vasoconstriction lasting from four to six hours on the average, but longer in a number of instances.

Side Reactions.—No side actions necessitating discontinuance of either antihistamine solutions were encountered. No systemic or latent irritation of the nasal mucosae were reported or observed. Approximately half of the patients on either solution developed temporary partial anesthesia of their nasal mucosae. Approximately 25 per cent of the patients complained about a mild transitory stinging sensation when the drops were instilled. About 20 per cent of the patients in both groups mentioned a dryness of the posterior nasopharynx following the application of these preparations.

Discussion.—There were no essential differences in the results obtained with prophenpyridamine maleate solution 0.5 per cent, and chlorprophenpyridamine maleate solution 0.25 per cent. Both of these solutions provided satisfactory nasal vasoconstriction in a high percentage of the patients with allergic rhinitis. The duration of vasoconstriction was considerably longer

than that usually observed with the non-antihistaminic vasoconstrictors. One of the most important desirable features of these preparations was their complete lack of causing a single incident of the "rebound phenomenon" commonly encountered with the prolonged usage of other types of vasoconstrictors. This lack of the "rebound phenomenon" was particularly outstanding in those patients employing one of these solutions daily for a period of from three to nine months. It was also noted that in no case was there any evidence that any patient became "drug fast."

The greater effectiveness of this mode of therapy for allergic rhinitis compared with the systemic administration of antihistamines is undoubtedly due to the higher concentration of the drug in the nasal tissues. Of further value, the local application of these antihistamine solutions diminished the likelihood of undesirable side actions which sometimes accompany systemic antihistamine administration.

CONCLUSIONS

1. Prophenpyridamine maleate solution 0.5 per cent and chlorprophenpyridamine maleate solution 0.25 per cent may be instilled with safety on the nasal mucosa.
2. There is evidence to show that these preparations provide sustained vasoconstriction of the nasal mucosa without the "rebound phenomenon" resulting from prolonged use.
3. Although these antihistamine solutions are not intended to substitute for accepted allergic diagnostic and therapeutic procedures, their employment in patients with allergic rhinitis provides rapid and effective palliation in the majority of these patients.

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CHEMICAL AGENTS UNSUCCESSFULLY EMPLOYED AS SUBSTITUTES FOR ACTH AND CORTISONE

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IT is axiomatic in the field of medicine that an important discovery spurs both research workers and clinicians to greater effort in extending or improving upon such discovery. The current medical literature testifies to the search for substitutes for cortisone and ACTH. An acceptable substitute should combine therapeutic activity with fewer side effects and at reduced cost of treatment. Several such compounds have been advanced and warrant consideration.

In November, 1949, Lewin and Wassén[8] reported an investigation on the effect of combined injections of desoxycorticosterone acetate and ascorbic acid in nine patients with rheumatoid arthritis. The treatment consisted of an intramuscular injection of 5 mg of desoxycorticosterone acetate, immediately followed by an intravenous injection of 1 gm of ascorbic acid. Five minutes after the injections the articular pain began to diminish and articular mobility to increase. In fifteen to thirty minutes the pain had practically disappeared, and the mobility improved as much as the anatomic changes in the joints and muscular atrophy would allow. All the patients reacted similarly. In some cases the improvement was astounding. The effect lasted from two to six hours, occasionally more than twenty-four hours. No toxic side effects were encountered. In some cases a drop in the sedimentation rate was observed.

The findings of Lewin and Wassén stimulated further investigation by a number of English workers, especially since supplies of cortisone were not readily available. Using similar technique, Hartfall and Harris[6] studied seventeen patients with rheumatoid arthritis. They reported four worse, one better, and the remainder as demonstrating only the improvement expected from simple physical treatment. Hart and Starer[5] treated five cases of active rheumatoid arthritis, giving three injections of desoxycorticosterone acetate and ascorbic acid daily for the first two days, two injections daily for another two days, and then one injection a day for a further three days. The dosage was that recommended by Lewin and Wassén. It was concluded that the injections produced a temporary euphoria which possibly played a large part in the improvement noted in two patients. In no case could the claims of great benefit suggested by Lewin and Wassen be confirmed.

A favorable response, striking and immediate, was found by Douthwaite[1]

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in four of five cases of rheumatoid arthritis. Pain was relieved and a sense of exhilaration experienced. The effect lasted only two hours on the first day. Treatment given daily resulted, by the end of a week, in relief up to seven hours. The most striking objective benefit was evidenced in the return of ability to flex the fingers and form a fist.

Spies, Stone, De Maeyer, and Niedermeier[11] obtained unfavorable results from similar therapy. They restricted six patients with rheumatoid arthritis to a low-sodium diet and gave 10 mg of desoxycorticosterone acetate intramuscularly and 1 gm of ascorbic acid intravenously each day without evident relief of symptoms. The ascorbic acid injections were then discontinued, but the injections of desoxycorticosterone acetate and the diet remained constant. Five days later three of the patients were prescribed ACTH in divided doses without their knowledge; the other three were given distilled water at the same intervals. Those receiving ACTH experienced prompt relief. The medication was then discontinued, and these patients promptly relapsed into the original condition.

Conversely, LeVay and Loxton[7] closely confirmed the observations of Lewin and Wassén. These investigators studied eighty cases of rheumatoid arthritis, and believe it unusual that this syndrome should resist response to all desoxycorticosterone acetate and ascorbic acid therapy.

My personal experience with desoxycorticosterone acetate and ascorbic acid therapy is extremely limited. McKendry, Schaffenburg, and McCullagh[9] treated twenty cases of rheumatoid arthritis and three cases of spondylitis at the Cleveland Clinic with combined desoxycorticosterone and ascorbic acid therapy. I had the good fortune to follow some of this work. The technique of Lewin and Wassén was adhered to closely. Of the sixteen patients who received more than two treatments, nine showed definite subjective or objective improvement. In two cases this improvement was maintained for only seven and fourteen days, respectively, despite continuing therapy. The authors emphasize the frequent observation that almost any form of treatment produces improvement in about 50 per cent of patients with rheumatoid arthritis. The improvement rate in their series does not exceed this proportion. No significant decrease was noted in the blood eosinophil count, which indicates the unlikely possibility of cortisone-like action.

Dr. Gamble, director of Physical Medicine at the Cleveland Clinic, and Dr. Corcoran,[8] of the Research Division, studied two patients with rheumatoid arthritis whom they placed on a low-salt diet, with large doses (up to 3,000 mg per day) of ascorbic acid given orally. The patients were followed for six months; although no remarkable results were obtained, they felt better, slept and ate better, and exhibited less fatigue. Objectively, there was definite improvement in joint motion as measured by the goniometer. These patients were able to tolerate physiotherapy exercises and hence were more suitable candidates for further joint therapy. Dr. Gamble

believes that such therapy may prolong the effects of cortisone after medication is discontinued and may possibly prevent some of the "rebound" phenomena.

Other adrenal steroids have been investigated. One of these, pregnenolone, has received considerable attention. Pincus' group[2] studied thirty patients with rheumatoid arthritis, to whom pregnenolone or pregnenolone acetate was administered orally in an average dose of 500 mg daily over a period of six weeks. Fifteen subjects showed a major degree of improvement, consisting of diminution of pain, decrease in swelling, increased mobility of joints, and increase in functional capacity. The improvement was noted within one to two weeks. Eleven patients achieved a mild improvement and four showed no change. In sixteen instances improvement was maintained for an average of six weeks after discontinuing treatment. No toxic effects were evidenced. They concluded that the relapse after discontinuing pregnenolone therapy is not as rapid as that after treatment with ACTH or cortisone. Pregnenolone, also, was found to reduce the sedimentation rate less rapidly and consistently than ACTH or cortisone.

Guest, Kammerer, Cecil, and Berson[4] reported that intramuscular injections of pregnenolone or pregnenolone acetate daily, or two or three times a week, resulted in no improvement in seventeen cases of chronic active rheumatoid arthritis. One patient with rheumatoid spondylitis improved objectively and subjectively, while a second case of spondylitis showed minor subjective improvement after one week's treatment; this was not sustained on continued therapy.

In a comprehensive article, Polley and Mason[10] reported the treatment of eleven patients with rheumatoid arthritis, using twelve steroid substances other than cortisone and four adrenal cortex extracts. Ten of these patients also received cortisone, ACTH, or both; such therapy acted as a standard with which to compare the effects of the other preparations. Each substance was prescribed without the patient having knowledge of its nature. Among the steroid substances tested were desoxycorticosterone acetate and pregnenolone, as well as compound F (of Kendall). Of the steroids investigated, the most minor structural alteration from cortisone appears to occur in compound F. The small supply of this steroid permitted administration to one patient only, for a twelve-day period. The sedimentation rate decreased significantly. The over-all relief of rheumatoid arthritis was an estimated 60 per cent as compared with 75 per cent relief from cortisone and 85 per cent from ACTH. The authors concluded that apparently the anti-rheumatic properties of the steroids are encountered only in cortisone, compound F, and adrenal cortex extracts containing significant amounts of these two steroids. In agreement with this conclusion are the investigations of Thorn and collaborators,[12] who state, "No agent has yet been produced that approaches the therapeutic efficiency of ACTH and cortisone."

In summarizing, considerable investigation has been made of other agents in a search for possible substitutes for ACTH and/or cortisone. Two steroids have warranted considerable attention—desoxycorticosterone acetate and pregnenolone. It seems probable that, at the present time, no acceptable substitutes are available for cortisone or ACTH.

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PERORAL PROPHYLAXIS OF POISON IVY DERMATITIS

(Continued from Page 171)

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

PASSIVE TRANSFER OF HYPERSENSITIVITY OF THE DELAYED TYPE

It is just ten years since Landsteiner and Chase[1] published their findings on the transfer of sensitivity to picryl chloride in guinea pigs by means of washed cells collected from the peritoneal exudate of the sensitized animal. As it turned out, it was to be the last major experimental contribution to immunology by Landsteiner.

Although the fundamental importance of these observations was quickly recognized, and although their impact was further emphasized by Chase's success in demonstrating transfer of tuberculin sensitivity by a similar technique,[2] it was only recently that Lawrence[5,6] developed the methods permitting experimentation along these lines in man. The transferring agent in this case is blood leukocytes, and the sensitivities which he succeeded in transferring are those to tuberculin and to hemolytic streptococci.

The resulting sensitization differs in two important aspects from that observed in the classical Prausnitz-Kuestner transfer of "reaginic" sensitivity.

1. The sensitization is not a local one but encompasses the whole body of the recipient. Thus, in the guinea pig the sensitizing cell suspension is injected into the peritoneum, and reactivity of the skin ensues. In Lawrence's work the leukocytes were intradermally injected, but the test for sensitization was made at sites remote from that of sensitization.

2. The ensuing reactivity is of the delayed (or "tuberculin") type and not of the wheal-and-flare type elicited locally by the Prausnitz-Kuestner technique.

Volumes of leukocytes in the order of 10^{-4} ml sufficed to effect sensitization. It must, then, be assumed that this relatively small number of leukocytes produces sufficient antibody for this purpose.

Evidence has thus been obtained for a postulate of long standing: namely, that in allergies of the delayed reaction type an antibody is liberated into the circulation which mediates body-wide sensitization. However, it should be understood that what has been transferred in these experiments is not the antibody (as is the case in the Prausnitz-Kuestner test) but the cellular elements which produce the antibody. It would be more correct to speak of a transplantation (of antibody-producing cells) rather than of a transfer (of antibody). It is of interest to note that similar "transplantation" of cells which produce "conventional" antibody has recently been reported: suspensions of cellular elements from lymph nodes were

obtained from guinea pigs and rabbits which had been injected with various antigens. Agglutinating or hemolyzing antibodies appeared in the serum of the recipient animals, which also were found to be anaphylactically sensitized to the corresponding antigen.[1,3]

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CONGRESSES TO BE HELD IN RIO DE JANEIRO

The XII Congress of the International Union Against Tuberculosis and the II International Congress on Diseases of the Chest sponsored by the Council on International Affairs, American College of Chest Physicians, will be held in Rio de Janeiro, Brazil, August 24-30, 1952. Both Congresses will be held under the Presidency of Professor Manoel de Abreau; Dr. Reginaldo Fernandes will serve as General Secretary. The Honorable Getulio Vargas, President of Brazil, has accepted the Honorary Chairmanship of the Congresses.

Physicians wishing to present papers at the Rio Congresses on the subject of tuberculosis are requested to write to Professor Etienne Bernard, Secretary General, International Union Against Tuberculosis, 47 Rue de Courcelles, Paris, France; and those wishing to present papers on nontuberculous diseases of the chest (heart and lung) should communicate with Dr. Andrew L. Banyai, Chairman, Council on International Affairs, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

For further information please write Mr. Murray Kornfeld, Executive Secretary, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

NEW WORK ON CLINICAL ALLERGY

To appear soon is a book entitled *Clinical Allergy* by French K. Hansel, M.D., F.A.C.A., Director, Hansel Foundation for Education and Research in Otolaryngology and Allergy, and Chief of Allergy Service, DePaul Hospital, St. Louis, Missouri. Doctor Hansel, with his thirty years of experience in the fields of otolaryngology and allergy, is well qualified to write this comprehensive volume. He has been working on it for the past three years. A review will appear in the ANNALS when the book is published.

The Editor's Page

A DECADE OF ASTHMA THERAPY

A farmer who could neither read nor write would frequently boast that he knew how "to figure." When challenged as to the usefulness of this accomplishment, he was forced to admit that it had some advantages but also its disadvantages. When on the road, for instance, he could tell how far he had travelled, but he could never be certain as to whether it was to town to which he wanted to go.

Any allergist who has any doubts as to how much we have learned about the treatment of bronchial asthma has only to consider the following papers as taken from the literature of two decades ago (1932-1942).

In 1933 Kairiukstis[12] treated his asthmatic patients with intramuscular injections of a preparation consisting of 10 parts of purified petroleum benzin and 30 parts of olive oil, which promptly counteracted the asthma attacks. The usual dose was 0.5 cc. The patients are reported as having lasting remissions and no ill effects. About the same time Shambaugh and Alter[26] were treating their asthmatic patients with postural drainage. Their series consisted of a group of severe recalcitrant asthmatic patients between the ages of six and seventy-five years, some of whom required no other treatment. Some had been asymptomatic for four years following inversion of the body for three minutes twice daily.

In 1935 the Pottengers[21] were treating asthmatic patients with both epinephrine in oral doses of 0.004 Gm three times daily and 0.5-1 cc of adrenal cortex extract in orange juice after each meal. In addition, each patient took sodium chloride 3-6 Gm daily one-half hour before meals. The sodium chloride by mouth produced "euphoria, improved intestinal function, . . . some diminution of the frequency of asthmatic attacks, and fortification of the effect of cortical extract."

At about this time, Wegierko[31] began treating asthmatic patients with insulin, 40 units before breakfast daily. The injections were repeated every three or five days, the patient's dyspnea diminishing in intensity, in some cases disappearing completely. Confirmation of this treatment by Hormann[10] was not lacking. This author found that 30-50 units relieved asthmatic attacks.

In 1936 Rosello and Plá[23] took patients who failed to respond to epinephrine, ephedrine, solanaceous drugs, atropine and morphine, and gave them instead intravenous magnesium sulfate in doses of 10-20 cc, with immediate salubrious effects. Some asthmatic patients were given magnesium thiosulfate with excellent results.

As recently as 1937 Dudan[3] was treating bronchial asthma with tubercu-

lin and sanocrysin, and Girbal[6] used oral and hypodermic liver extracts with good effect. He reported that in all the asthmatic patients signs of hepatic insufficiency could be found, and that liver and also cholagogues were indicated.

During the next two or three years, a number of papers concerned with nonspecific treatment were published.

Naef[20] gave asthmatic patients intramuscular doses of stock-mixed pertussis and mixed catarrhalis vaccine, the interval between injections being forty-eight hours and seven days. The report shows that 68 per cent of the patients had complete inhibition of their allergic spasm, with an additional 18 per cent showing some improvement. In only 14 per cent was there no response.

Hardeck[7] used "Pyrifer," a nonpathogenic colon bacilli vaccine, in thirty-four cases. Koeniger[14] reported excellent results with "Peptosinalb," consisting of a 5 per cent alcoholic fraction of Witte's peptone and 1 per cent novocaine, while Van der Rois[29] achieved equally good results with "Pavyco," which consisted of papaverine, Eumydrin, Phenacetin, and barbiturates.

Gold therapy was quite popular, and in 1938 Sangiorgi[24] reported satisfactory results in forty cases of bronchial asthma treated for more than a year. Some patients were also given tuberculin, and others, insulin shock. Histamine was being used for treatment, but with good results in only three of sixteen patients.

At this time, in Germany, patients were being treated with a proprietary preparation by Minibeck.[19] The mixture contains among other things calcium, glycerophosphate, calcium lactate, potassium iodide, potassium bromide, ferrous lactate, and sodium bicarbonate.

In 1938 stellectomy was popular, and Leriche and Fontaine[16] reported on the treatment of fourteen patients with bronchial asthma, in all of whom there was an immediate disappearance of the bronchospasm following bilateral stellectomy, with definite improvement in three others. Malherbe[17] obtained equally good results with procaine infiltration of the stellate ganglion.

Further results in the treatment of bronchial asthma with insulin shock were reported by Minet and Warembourg,[18] who reported that twelve to fifteen shocks were usually required for "cure." All but two of their series of patients had remissions for one to two years.

During this same period bronchial asthma was being treated by Hemen[9] with "Paspat," a bacterial vaccine containing also anterior pituitary hormone. The results were "excellent." In 1939 Vollmer[30] was able to confirm the good effects of insulin shock in seven children, in whom the asthma was relieved for an indefinite period of time. In the same year (1939) Farmer reported on ethyl urethane in doses of 2-4 grams daily alleviating the asthma attacks in fourteen patients of a series of thirty.

As recently as 1940 Dopffel and Kutschera[2] reported on Eupaverin as

relieving the attacks of pectoris and bronchial spasm, while Haury[8] was proving that hypomagnesemia is associated with bronchial asthma, magnesium sulfate, given parenterally, relieving asthmatic attacks for 18-24 hours.

Dolantin, which was being used with good effect in angina pectoris and cholelithiasis, was reported by Erlendsson[4] as being a good and reliable antispasmodic agent for patients with bronchial asthma. Meanwhile Capani[1] was treating fourteen patients with urine gonadotropic hormone (prolan), with nine of the patients reported as "completely and definitely cured," while the others showed improvement.

In 1940 nonspecific forms of treatment were many. Schimert[25] treated fifty asthmatic patients with colloidal copper in doses of 10-100 gamma. He stated that there was complete disappearance of the attacks in twenty-one and marked improvement in an additional seventeen. The most innocuous of such treatments was that reported by Prince,[22] who gave his patients oral dextrose. There was a striking response to such therapy, other sugars being without effect in relieving asthma.

Sokal[27] had no explanation for the success of his treatment in giving pertussis vaccine to six patients with severe bronchial asthma. All improved within forty-eight hours following the first dose and were relieved when the vaccine injections were repeated.

The stellate ganglion came in for more treatment by Tapella,[28] using alcohol in ten patients, who responded by remaining free of symptoms for three to eighteen months.

King[13] found that he could relieve all of his patients of their asthmatic attacks by intravenous injections of strontium chloride (15 gr in 10 cc).

The insulin shock therapy came back into the headlines in 1941, when Wilken-Jensen[32] reported on nine more patients treated by hypoglycemia. He stated that "asthmatic states were always cured." The attacks of dyspnea were in five cases stopped or reduced to few and small attacks during the observed period (up till four months), the expectoration was stopped or diminished, and the use of drugs and pills was stopped or reduced.

Lamson and Bacon[15] reported on the 153 asthmatic patients who had never obtained satisfactory relief from other methods of treatment and were, therefore, given theophylline monoethanolamine, all but 10 per cent being relieved. Unexpected beneficial side effects were observed, this drug controlling nasal symptoms, with or without asthma, and such refractory conditions as urticaria and angioneurotic edema.

In 1942 Jimenez Diaz[11] used "desensitization with antitetanic serum." By producing repeated mild shocks, the author was able to control the asthma in three patients, in whom all other therapeutic methods had failed.

Like the farmer, this brief review has given us some idea of how far we have come. It does not tell us, however, whether we are on our way to a place to which we want to go.

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AMERICAN COLLEGE OF CHEST PHYSICIANS

The Eighteenth Annual Meeting of the American College of Chest Physicians will be held at the Congress Hotel, Chicago, Illinois, June 5 through 8, 1952. A scientific program covering all recent developments in the treatment of heart and lung disease is being arranged.

Progress in Allergy

MISCELLANEOUS ALLERGY

A Review of the Literature of 1951

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The specialty of allergy has withstood the test of time. One of the most thought-provoking publications during the past several months is that on the general subject of allergy as written by Jonathan Forman.[55] In this article the author has tried to give the physicians of America a clear concept of what allergy is and what it is not. He has succeeded very well. Variations in our environment produced by modern living have put a great strain upon our autonomic nervous systems. These variations have produced imbalances of this nervous system and, therefore, have increased our disposition to develop allergic diseases. He has presented a working theory of allergy that is understandable to the uninitiated and will serve as a basis for explanation by those who are more advanced in this field. In the 10 per cent of our population who have certain bodily defects as a result of inheritance, undigested or partially digested protein does manage to get into the system and, therefore, must be handled by cells that have not been introduced to these substances in previous contact. On the theory that "the cell never forgets," Forman goes on to explain that many tools for the digestion of that particular offender have been produced should it ever enter the system at a later date. These tools have been designated as antibodies, and stock piles of these so-called tools are set up at the usual point of entry. The detection of these stock piles, especially in the skin, is the basis for the skin test reaction and also is a defense mechanism should the offender gain entrance to the system at a later date. Forman's description of the allergic reactions would tend to lead one into the belief that this reaction in itself is truly a defense mechanism and, as such, it can be accepted. The production of mucus in the respiratory and alimentary tracts is an effort to enmesh the offending substances that are trying to gain entrance into the body. The location of this struggle between the defense mechanisms and the offenders is the prelude to the symptoms of hay fever or asthma or colitis or headache. A person living today has a great many more chances to gain an allergy than did our ancestors. This results from the industrialization of our country with the production of many substances that are used today to which many persons do become allergic. The influence of air conditioning and travel have also aided the apparent increase of allergic diseases. This same industrialization has brought us into contact with many solvents, resins, metals and oils to which the cells of the skin can and often do become allergic. Forman has proceeded to describe and explain the more commonly recognized forms of allergic disease such as drug sensitivity, contact dermatitis, atopic diseases, and nonatopic allergies. He has also delved into the secondary or predisposing factors and mentions these as being temperature changes, emotional upsets, fatigue, infections, various deficiencies—malnutrition, endocrine deficiencies—as well as barometric changes. He stresses the fact that there are no short cuts to either a diagnosis or to the proper treatment of the allergic patient. The reader of this review is referred to the original article for a very pleasant few minutes of reading on an extremely interesting subject. A critical review of this same paper has been noted by an anonymous author[2] who feels that the allergist should not forget the fact that allergy is basically an immunological

phenomenon. This author calls the allergist to task for applying the label of allergy to any nondescript or ill-defined condition for which no other explanation has existed.

The inroads that various fads and fancies have made into the specific management of the allergic patient have also been the basis for publications by other authors. Feinberg[47] has successfully attempted to explain some of the common misconceptions that may enter the minds of those not familiar with the basic concepts of allergy. He very capably refutes the opinion that allergy is a fad and that its concept is unnecessary in therapy. It has been amply proven in numerous series of allergic patients that proper allergic management can be carried out to completion and that the results are infinitely better and more lasting than with symptomatic management. The argument that every positive skin reaction calls for desensitizing injections is refuted by this same author. He adequately explains the difference between significant positive skin tests and those that may be considered as flares or nonspecific reactions. He emphasizes the fact that it must be remembered that skin reactions as well as clinical allergy follow the pattern of biologic relationships. With such an understanding it will be reasonable to believe that a person sensitive to ragweed need not be treated specifically for his goldenrod or daisy pollen skin test reactions. These latter pollens are not insect borne and, therefore, the patient may have never been exposed to these substances in spite of his positive reactions to them. The difference in testing extracts, dermatographism, contaminating substances in the extract, and inexperience of the operator will often lead to the reporting of multiple reactions. Another popular misconception is the supposition that if skin tests are negative, the complaint is not allergic or allergic management is not possible. Further discussion of popular misconceptions have been covered quite adequately by this author. He successfully explains why a laboratory or pharmaceutical house cannot furnish a treatment set based on the number of "plus marks" following a reactive antigen. At the same time, a desensitizing schedule cannot be preformed adequately for any patient. This emphasizes the individualization of diagnosis as well as treatment of any allergic disease. The erroneous concept that a short course of desensitization will cure an allergy is based upon the relative ease with which a laboratory animal may be desensitized. Even though desensitizing therapy has proven to be beneficial, it should be recognized by the physician and the patient that the undertaking is a long process, and at best may be only partial. The recent attitude toward the beneficial effects of antihistamines, corticotrophin, and cortisone therapy constitutes specific examples that "the newest ideas and newer therapies are the best." In refuting this misconception, Feinberg mentions other forms of therapy in the past which have been faddish and short-lived. It is a mistake to assume that just because the nature of a disease is not explained by any other means that allergy is the cause of the symptoms.

Kern[71] has followed much the same line of thought in a discussion of the diagnosis in allergic states, with emphasis on its principles and pitfalls. The most important feature in the diagnosis of any allergic disease, according to this author, is the recognition of the allergic nature of a given illness and the suspicion in the clinician's mind that this possibility does exist. He adequately describes and presents the various allergic diseases for the respiratory and gastrointestinal tracts, those which will affect the cutaneous element and the other systemic manifestations of allergy. His diagnostic procedures consist chiefly of a personal and family history, a physical examination, the usual laboratory aids, and skin testing. He makes a point to stress that the skin test does not reproduce clinical exposure in that many foods are eaten only in a cooked state and hence have lost some of their antigenic capacity. He feels that one should set no undue store by the size of any given reaction, nor does a positive skin test mean that it is definitely responsible for the patient's symptoms.

He is of the impression that the commonest cause for the failure in the treatment of an allergic condition is the inadequacy with which the patient carries out the instructions that have been given. This is not offered in the way of an excuse. It is stated only to emphasize to the practicing physician the need of adequately describing the measures that should be followed and the point of completeness that should be obtained. The continuation of symptoms may also be due to a failure to complete some important therapeutic procedure that has been overlooked by the physician. Other continued symptoms may be due to an incomplete diagnosis and the failure to discover an offending allergen or allergens that may complicate the picture in its entirety. This same author[72] is of the opinion that the diagnosis of allergic disease in the aged calls for greater care and skill than at any other time of life. Likewise, the treatment of allergic disorders in the aged patient demands in full measure the best application of the physician's art. The treatment, therefore, must be suited to the whole patient and not merely to the allergic disease. The use of skin tests in the aged patient is met with minor or even negative reactions in the face of known clinical sensitivity. It is for this reason that the diagnosis of asthma as an intrinsic disease is often noted in the aged patient. Kern is of the belief that a sensitivity to external allergens, if proper and thorough search is made, can be established as a factor in the majority of patients whose asthma begins even in old age. His arguments would tend to refute other opinions that extrinsic asthma seldom begins after the age of forty-five or fifty years. The correction of an allergic disease by avoiding its antigenic cause can do much to help an overburdened circulation that is frequently found in the elderly patient. The shifting patterns of allergic excitants form the basis for an editorial by Spain.[120] Etiologic factors fluctuate in importance as their incidence rises or falls. The change of the nation from an agricultural to a manufacturing era results in the supplanting of materials of animal and vegetable origin by substitutes or replacements of products of metal, synthetic, resin, or fiber source. This editorialist feels that with many of its chief ingredients being used less frequently the disturbing influence of house dust as an allergen is definitely impaired. He reviews the past importance of such factors as horse dander, orris root, various other animal danders, cotton, kapok, and silk. The dilemma caused by the use of therapeutic horse serum in the past is not with us in present-day practice to the point of importance, since the diminishing use of this and other animal sera has lessened the incidence of serum accidents. The speed of travel today has influenced even the pollen and mold seasons and the extent of their spread. He cites the importance of occupational dermatitis due to substances which were unknown a few years ago. Drug sensitivity is also mentioned by this author. He feels that the allergist should change with the times.

Changing times also have introduced many new therapeutic measures to the field of allergy. Though they should no longer be classified as "new," the antihistaminic preparations are still the source of many publications. Wyngaarden and Seevers[138] have reported the toxicity of antihistaminic agents, particularly from the standpoint of serious fatal reactions. They have collected a series of eleven cases of fatal intoxication and have also discussed serious reactions with recovery from marked overdosage. Toxic or fatal reactions have been chiefly due to accidental overdosage. The most striking example of death resulting from these drugs is noted in the susceptibility of children to the convulsive properties of these compounds. In contrast, they have noted that convulsions in the adult are more uncommon, while depressant effects are more serious. Of the eleven fatalities reported, eight were in children under the age of two years and five of the eight were accompanied with convulsions. The three fatalities in adults occurred from central nervous system or bone marrow depression. Other than the above, there have been noted some unusual reactions with peculiar idiosyncrasies occurring in allergic persons. Treatment at

the present time seems to be chiefly symptomatic. The therapy of the serious reactions depends, of course, upon the type of reaction that is encountered, whether it be depressant or convulsive. The responsible antihistaminic agent, of course, should be stopped at once. The authors call for the use of these drugs only under the guidance and supervision of a physician.

Fishbein[53] has reviewed the antihistamines in a special article. He discusses the action of histamine and the other preparations in this classification. He also devotes some paragraphs to the mechanism of allergy and to the indications for the use of the antihistaminic drugs. The side effects as described by this author are the usual ones that have been reported or noted by most of the men practicing allergy today. The real difficulty in interpreting the reports regarding the toxicity of any of the antihistaminic agents rests in the different degree of reactions that many patients will exhibit. Even the individual patient will not react with similar responses to the same or different medications. He asserts that the antihistaminic preparations are of little value in bronchial asthma though there may be some advantage to their use in this disease when the preparations are combined with epinephrine. He advocates a more careful labeling of these materials to clearly state the limits of dosage as well as the possibility of any toxic side-effects when these limits are exceeded. Silbert[116] has reported the results of a study using combinations of ascorbic acid and antihistamines in the treatment of a variety of allergic diseases. He did not include allergic asthmatic bronchitis in this study. The results seem to indicate, according to this author, that the combination of ascorbic acid and antihistamine is much more effective than when the latter material is used alone. He found that relief was more prompt and the duration of that relief was somewhat more prolonged with the combined dosages. Of the one hundred and thirty-one patients used in this study, seventy-four of the group received tablets containing 25 mg of Thephorin and 200 mg of ascorbic acid. Fifty-seven received tablets containing a mixture of ascorbic acid (250 mg) and Chlor-Trimeton (2 mg). He was of the impression that the vitamin C had a potentiating effect upon the action of the antihistaminic preparations. As a result of this effect, it was possible to increase the interval between doses as well as to reduce the incidence or occurrence of any side-effects. In this same line, Shure and Harris[115] were struck with the great number of antihistaminic drugs on the market today. They were also impressed with the prevalent action of combining these agents with other drugs to make them so-called "antihistaminic plus" compounds. They feel that the latter combination is an admission on the part of the manufacturer and other workers that the antihistamines alone are lacking in effectiveness to a good degree. They note that the combination of antihistaminic preparations, ephedrine, and aminophylline has been used and found of good value in the treatment of bronchial asthma. It has always been the opinion of this reviewer that when these preparations were used in the therapy of asthmatic symptoms, the real relief was obtained from the aminophylline and the ephedrine rather than any beneficial effect being the result of antihistaminic action. These authors have tabled in good detail the antihistaminic preparations that are of most common use at the present time. They describe them as to their origin, their size, and their probable action. The essayists are of the opinion that the antihistaminic drugs are of most value in preventing rather than altering an existing pathologic state.

Ratner[107] also calls attention to the serious side-effects that may result from the use of antihistaminic preparations. In an editorial, he reports that death in one child was due to cardiorespiratory failure with autopsy findings being similar to those due to heat stroke. Regardless of the fact that these drugs are sold over the counter, the individual tolerance may differ widely in various patients. For that reason Ratner warns against the indiscriminate and careless handling of these materials within the reach of small children. He advises that these drugs be used

under the direction and at the discretion of the attending physician. Wittich[137] feels that Chlor-Trimeton maleate repeat action tablets (dosage—8 mg each) proved to be very effective in the symptomatic treatment of respiratory allergy. His patients included those complaining of perennial bronchial asthma as well as seasonal asthma and hay fever. The effective dosage was an 8 mg tablet at twice daily intervals. He was of the opinion that the repeat action medication possessed a distinct advantage over the smaller dosage in the plain form. He was somewhat surprised to find that these repeat action tablets also had a beneficial effect upon the patient suffering from an acute head or chest cold. In many instances the patients, not being aware of the type of medication they were receiving, requested the antihistaminic tablet in preference to the usual measures used in the treatment of the common cold. Only two patients of his series were forced to discontinue the drug because of any reactions. Toxic symptoms disappeared after the use of the tablets for a day or two even though the medication were continued.

Cullick and Ogden[28] have reported a controlled clinical study with Perazil. The dosage of the preparation in thirty adult patients varied from 50 to 100 mg daily. A variety of allergic symptoms were found, and the above drug was used in the treatment of the symptoms. Those under specific treatment received only Perazil and placebo on alternating weeks. Six of these thirty patients reported toxic effects but three of these were noted while the patient was receiving placebo medication. These authors were of the opinion that Perazil was a longer acting antihistaminic drug than the others that had been in use. Their percentage of side reactions was definitely lower than with other drugs. They felt that this was due to the prolonged action of the drug with the necessary administration of the tablet being less frequent. In the opinion of Sherman[113] the antihistaminic drugs should be classified as to the maximum therapeutic benefit to be derived from each preparation. He believes that the use of these drugs in any disease is not one to be associated with any curative properties. The reaction from the use of each preparation is rather uncertain. The advantages of using a longer acting material are also described by Spielman.[121] He has reported that one oral 50 mg tablet of Perazil seemed to give benefit in the majority of allergic symptoms with a minimum of toxic disturbances. The side-effects were noted in only 4 per cent of the seventy-three patients. The action was noted to be over a period of twenty-four hours. This author recommended this drug in association with other measures of more specific properties. A total of 296 patients with a wide variety of allergic complaints were observed from three days to fourteen months while they were receiving Ambodryl. The results in this survey are comprised in a very interesting report by McGavack et al.[88] Of fifteen patients in this group with acute urticaria, twelve obtained complete relief in approximately one half the time it usually takes for such lesions to disappear spontaneously. It was found that when sufficient Ambodryl was taken, the offending allergen could be encountered without fear of an attack. When the attack was present, the symptoms were shortened by at least 50 per cent. Of 131 cases of seasonal hay fever, 127 received satisfactory if not complete relief of their complaints. Nine and nine-tenths per cent of these patients with seasonal hay fever failed to obtain any relief of consequence. Nonseasonal allergic rhinitis was much more difficult to control with this preparation. The authors felt that Ambodryl was of some definite benefit in preventing asthmatic attacks. They also expressed the opinion that this drug, with its atropine-like action, may be of some value in the definite suppression of the symptoms when they are present.

It must be understood that the enthusiasm for these preparations in various conditions rests with the results obtained. It is unfortunate that similar good results cannot be reached by all investigators using similar preparations. The sedative action of Benadryl makes it a valuable adjunct in the treatment of narcotic withdrawal syndrome, according to Vaisberg.[132] The drug was used in its injectable

form, thus permitting a reduction in the amount of narcotic required for the addict. It seemed to have a potentiating action when used with narcotics and, therefore, the dosage of the latter preparation could be reduced when it was required by addiction or for the relief of pain. The prolonged use of the antihistaminic drugs has been thought to lead to some degree of tolerance. This point was the basis for a very interesting study by Dannenberg and Feinberg.[29] Such tolerance was usually developed after a maintenance dosage of the antihistaminic tablet for a period of seven to twenty days. Such tolerance development was determined by noting the inhibition of histamine and antigen reaction of the nose, skin and eyes following an oral dose of an antihistaminic substance. Those patients who developed tolerance to an antihistamine, as measured by histamine, also showed it when tested with ragweed. Those who showed such tolerance in skin testing also showed similar tolerance development by mucous membrane tests. The chemistry of the antihistaminic drugs is sufficiently varied to suggest that tolerance on chemical grounds is quite unlikely. The authors feel that the tolerance has to do with the common pharmacologic action in this series. This investigative study revealed that partial inhibiting ability of the drug began to appear at the end of seven days and no further tolerance was apparent after fourteen days following the cessation of the use of the preparation. It is suggested that the development of such tolerance should require increase in the dosage of the drug or a discontinuance for a short period before resuming therapy. This would permit such tolerance to be overcome. Twenty of twenty-eight patients studied by MacPherson[86] reported excellent relief from the pain of dysmenorrhea with the use of antihistaminic drugs. With the administration of the medication in the first twenty-four hours of the menstrual cycle, relief was quite definite and prolonged. The author therefore suggested that such dysmenorrhea might be upon the basis of an allergy to uterine secretions. To the more conservative allergist, this would be somewhat far fetched.

The use of antihistaminic drugs in the treatment or interruption of the symptoms of the common cold is the basis for a committee report regarding public health.[23] Since the symptoms of the common cold vary as to cause, season, patient susceptibility, and many other factors, there was extreme difficulty in judging whether or not patients were responsive to these materials. The antihistaminic drugs may be of some relief in the therapy of the common cold if the symptoms are caused by an allergic response. However, if the symptoms are definitely due to a virus or a bacterial invasion, then such benefit is not to be expected. The fact that placebo medication gives apparent relief is a base for the questionable value of this medication. Though it is recognized that severe reactions to these drugs are rather uncommon, the indiscriminate use of them for the symptoms of a common cold is not to be advised. The serious side-effects of antihistaminic usage have been noted in many publications to be frequently exerted upon the nervous system, though they also have an effect upon the heart and the digestive tract. Serious damage to the white blood cells has been traced on some occasions to the use of these preparations. One of the greatest disadvantages is the fact that symptoms which appear to be only those of a "cold" may be the initiation of a serious infection. Because of the use of these drugs the infection may be neglected until the condition is one of very serious nature. It was the combined opinion of the Committee on Public Health Relations of the New York Academy of Medicine that the antihistaminic drugs were of no value in the treatment of true colds and that the public should be warned as to the hazards associated with their use. In direct opposition to this report are the noted beneficial effects of one such drug in 2,199 cases. Tebrock's[127] patients were stated to be in the initial days of a common cold. All of these patients were treated on a therapeutic basis, and no prophylactic nor placebo studies were conducted. Seventy-five per cent responded very well to treatment, being free of symptoms within seventy-two hours. Only eighty-four instances (3.8 per cent) of

side effects were noted in these cases with the use of Neohetramine. The drugs were not continued for a prolonged period of time because the therapeutic effectiveness was thought to be present only when the drug was taken early. The author has stated that the effectiveness of the drug is also dependent upon the dosage of the tablet and inversely proportional to the lapse of time following the onset of symptoms. If treatment were instituted forty-eight hours after the onset of symptoms of a common cold, the drugs were thought to be definitely ineffective. Tebrock did not feel that the antihistamines were a cure for the common cold but that their effectiveness was definitely one of symptomatic value. Most of the reports for the effectiveness of these agents in the treatment of the common cold have lacked adequate controls. The investigators have relied solely on subjective evaluation for diagnosis and effective treatment.

An editorial[35] summarizes the pros and cons of those observers interested in this controversial question. In the early days of the investigation with the use of these drugs, most of the workers credited definite benefit to the use of these preparations in the treatment of the cold. Recently the pendulum has seemed to swing in the opposite direction. This editorial also calls attention to the serious side reactions that can be expected in a small percentage of patients. A careful control of all investigative work is the plea of this article. Fowler[56] has observed that a specific hypersensitivity and imbalance of the involuntary nervous system is a fundamental feature in the allergic type of cold. The symptomatology of this syndrome also seems to be associated with histamine or histamine-like substances. He theorizes that if antihistaminic drugs have any effect upon the infectious head cold, they do so by blocking secondary parasympathetic responses and thus producing symptomatic relief. The infection may also release histamine, which is reduced in action by the use of the antihistaminic materials. Failure of the antihistaminic drugs to relieve the symptoms of a common cold in boys at a summer camp forms the basis of a report by Fisher.[54] He found that the results were no better with placebo medication than with an antihistaminic tablet. The side reactions were no more in evidence with either preparation. Of one hundred patients treated, some were given an antihistaminic drug (Tripelennamine hydrochloride) and others were given white lactose placebo tablets. Similar findings of the effect of antihistaminic-placebo treatment of the common cold have been reported by Lowell and his co-workers.[85] These drugs were given to 729 patients in a dosage of two tablets at the onset of symptoms and thereafter one tablet daily for eleven doses. The medications used were Trimeton, Neo-Antergan and Neohetramine. In Browning's report[17] a group receiving placebos had the lowest rate of hospital admission and the fewest number of days of care per student hospitalized. The antihistamine used in this study was 50 mg of Histadyl, every four hours for as long as cold symptoms persisted. The study of 600 subjects comprising this report covered a period of one year. The average number of colds and the duration of symptoms were the same regardless of whether the patient received the antihistamine, the placebo, or no treatment. Attention was called by Fabricant[45] to the high incidence of side effects attributable to antihistaminic drugs in treating common colds. He formed carefully controlled studies on 213 university students with six different drugs and placebos. This investigator concluded that antihistaminic drugs were of no more effectiveness than were placebos in aborting the symptoms of the common cold. He could find no validity in the contention that these drugs possessed an effectiveness regardless of the early administration following the initial symptoms of the acute head or chest cold. One of the first reports to indicate the failure of the antihistaminic drugs to prevent or cure the common cold was made by Feller and his associates.[50] Volunteers were given 50 mg of either Pyrrolazote or Neohetramine four times a day for five days. A similar group were given placebos. Two to twelve hours after the first dose all these volunteers were inoculated with the dilute nasal secretions of patients suffering from true common

colds. The results of this investigative study showed that the antihistamines did not prevent nor alter the severity of the symptoms produced by such inoculation.

The reports of DeGara[33] would tend to indicate that elevation of blood histamine is not a necessary component of allergic disease. He has noted that blood histamine levels of 8 gamma or more were found most frequently in allergic conditions, but none of his seventeen patients had levels exceeding the range found in healthy individuals. The lowest levels of histamine in the blood were found in patients suffering from rheumatic fever. Histamine levels above 8 gamma per cent were noted in collagen diseases. This latter figure, however, was lower than that observed in allergic conditions. He surmises that if the antigen-antibody reactions were largely responsible for the elevated blood histamine levels, the findings should be noted in the early part of each disease. In rheumatic fever, however, the elevated findings were usually noticed in the late or proliferative stages of this condition. The normal range of histamine blood level is reported to be between 2 and 7.3 gamma per cent. It is recognized that there is no association between the level of histamine in the blood and the amount of circulating eosinophils. Traina[130] attempted to determine whether folic acid would inhibit histamine shock in guinea pigs. His results would indicate that folic acid, when used in sufficiently large dosages, would have some antihistaminic activity. This was stated to be limited, however. Because of the inability of the folic acid to prevent the shock with a large dosage of histamine, Traina is of the belief that the histamine released during anaphylactic shock must approximate one lethal dosage. This has been stated to be 0.4 mg per kg. Intravenous procaine was used for the relief of joint pain, pruritus, jaundice, and rheumatoid arthritis with good improvement by Boyer, Barwick and Meidt.[11] The patients were tested preliminarily for possible sensitivity to the procaine. If the skin test reaction were negative, 1 gm of procaine in 1,000 ml of normal saline or glucose was injected intravenously. No general reactions were noted from the administration of this solution. One gram of procaine daily for two to three days seemed to be sufficient to give lasting improvement in those patients suffering from penicillin reactions.

That the action of procaine may be prolonged over a very few minutes is rather adequately explained by Hall.[62] He has stated that when procaine is administered intravenously, it will be found in traumatized or inflamed tissue in a concentration eight times stronger than that found in normal tissues. The hydrolytic products of procaine usually appear within twenty minutes and, therefore, any delayed reaction is impossible. Procaine is quickly hydrolyzed within a very few minutes to form p-amino-benzoic acid and diethylaminoethanol. The former product is acetylated, and 94 per cent of this is excreted in the urine within twenty-four hours. The fate of the latter product is unknown. Because of the quick hydrolyzation of this preparation, a delayed reaction is considered to be an impossibility. The dosage of procaine is usually determined with the thought of concentration and the rate of administration in mind. However, the amount of drug should not exceed 4 mg per kg of body weight at any one administration. There are signs and symptoms of intolerance that may be noted during administration of procaine. These are somewhat similar to histamine flushing, relaxation, occasional apprehension or sleepiness. This author follows the rule of the "procaine unit"—the amount of procaine calculated at 4 mg per kg of body weight in a 0.1 per cent isotonic saline solution that is given in twenty minutes. Should there be any immediate reaction from the administration of the drug, Pentothal sodium is a suitable and adequate antidote. In the past, procaine has always been thought to have various actions that are chiefly, from our standpoint, beneficial in most allergic conditions. These are considered to be antihistaminic as well as anti-acetylcholine. Procaine also has some direct action on cells, particularly nerve and endothelial cells. Some authors and workers feel that procaine has an epinephrine-potentiating action. It is this latter function that makes

procaine of some definite value in the relief of acute asthmatic attacks, even though such relief may be noted only during the administration of the drug.

Kerr and Brehm[73] have reported no instance of sensitivity, reaction or convulsions being observed in a series of 271 injections of intravenous procaine. These authors have reported that the early administration of intravenous procaine seemed to prevent the development of full-blown serum sickness. Its chief advantage in allergic dermatitis has been the almost immediate relief of pruritus. The two potentially serious reactions that may occur from the use of this drug are convulsions and cardiac arrhythmias. Addition of glucose or vitamin C to the solution seems to reduce the incidence of convulsions. These serious reactions usually occur as a result of too rapid injection of the solution. They may be satisfactorily controlled in most cases by either stopping or reducing the rate of flow. Kerr and Brehm stated that uncertain results should be expected from the use of intravenous procaine in cases of bronchial asthma inasmuch as the relief to be expected is dependent entirely upon the factors producing the bronchospasm.

When histamine is given intravenously for treatment and relief of foreign protein type reactions, the dosage and interval between treatments must be individually adjusted for each patient. Prince and Etter[101] were successful in relieving seventy-eight of eighty-one patients with severe foreign protein reactions. In all of these, the antihistaminic drugs had previously proved to be ineffective. Most of their patients were those with penicillin-type reactions. Of the eighty-one patients, sixty-two of them were in this class. About one fourth of the reactions occurred immediately or within twenty-four hours, another one fourth on the seventh day, and another one fourth on the fourteenth post-injection day. These authors found that the average patient was in better condition and more comfortable with injections of intravenous histamine given every four to six hours. On some occasions the administration of histamine was given in a continuous flow. As improvement was noted, the frequency of injections was reduced. The administration of histamine by intradermal route gave very good relief in those patients whose veins were not satisfactory for intravenous use. The one disadvantage to the intradermal route is the lack of control of the response. No undue side-effects were expected nor found by Prince and Etter with the use of intradermal histamine. The flushing dosage could be established by skin-test titration. They eventually attempted first to flush each patient with an intradermal dosage, and if this were impossible, then the intravenous route of administration was used. In the past, it has always been thought that bronchial asthma was a definite contraindication to the use of histamine preparations. These men found that patients with histories of asthma did not notice any increase in the severity or aggravation of their asthmatic symptoms. In three patients with questionable asthma, the histamine was discontinued because of an aggravation of the symptoms, but in these the complaints had been asthmatic bronchitis rather than true atopic bronchial asthma. The continuation of dermatographism or the presence of chronic urticaria following a penicillin type reaction were common findings in their series. They postulate that the persisting skin lesions in chronic form would indicate that the reaction has lowered the threshold to the point where previous subclinical factors have become operative. They also noticed that histamine seemed to possess some diuretic effect and felt that this was probably due to a mobilization of edema fluid from the kidney parenchyma.

Horton[68] has probably done more work with the clinical use of histamine than any other investigator. It is his opinion that the common denominators of allergic disease are localized vasodilation, altered capillary permeability, and the resulting edema that has been provoked by the local release of histamine. It has long been recognized that histamine is the most powerful vasodilator yet known. It dilates the arterioles, venules, and capillaries. There is no direct effect of histamine upon the cardiac action, but the output and rate of the heart are both increased as a reflex response

to the above mentioned vasodilation. Horton has reported that many of the phenomena observed after the clinical use of cortisone and ACTH have been noted after the clinical use of histamine. Horton's case illustrations and the discussion-comments on each problem are indeed worth review and study by anyone interested in the field of allergy. The similarity between the results obtained with intravenous histamine and those following the administration of ACTH and cortisone is the basis for Horton's expression that histamine does cause the release of these hormonal agents. This reviewer has had the opportunity to use both intravenous and intradermal histamine in many instances. The best results have been noted in the serum type reactions and in histaminic cephalalgia. It is my opinion that though its variety of actions would tend to indicate its use to be beneficial in a variety of conditions, the more conservative view is to be advised.

Local atrophy of subcutaneous tissues secondary to injections of protamine zinc insulin was observed in two cases by Rafool.[105] In an effort to correct this apparent sensitivity, various measures were undertaken. No atrophy resulted in these two patients when regular insulin was substituted for the former type. No atrophy was noticeable when mixtures of regular and protamine zinc insulin were used. Globin insulin did not produce atrophy in either patient. The subcutaneous tissue atrophy was noted regardless of the type (Squibb or Lilly) of insulin that was employed. The author felt that the sensitivity of the patient to the protamine zinc fraction was responsible for the atrophy inasmuch as no definite evidence of direct insulin sensitivity was established. Spoont and Dyer[122] have reported the presence of urticaria following insulin injections. The urticaria occurred both locally and in general distribution. The lesions were not improved nor relieved with antihistaminic substances, whether they were given orally or in conjunction with the insulin by subcutaneous administration. Their patients had positive skin test reactions for various insulin preparations, regardless of the source or type of material. There was less local erythema to crystalline insulin than to the other forms tested. Attempts to desensitize the patients met with failure.

To the uninitiated, the etiology of purpura is seldom considered to be upon an allergic basis. Highstein and Zeligman[66] have reported the presence of a purpuric rash of six months' duration which was proven to be due to the menthol in medicated cigarettes. When the mentholated cigarettes were discontinued, the rash cleared quite rapidly. However, a reappearance of the purpuric lesions was noted following the ingestion of menthol by mouth. All blood studies on this patient were normal except for an increased bleeding time during the period of the purpura. The usual side-effects found in antihistaminic ingestion are well known to most students. An unusual reaction to the ingestion of these preparations is a case of purpura simplex reported by Uvitsky.[131] The ingestion of one Pyribenzamine tablet three times daily for a period of three days produced the appearance of small purpuric lesions on the legs of the patient. She had previously noticed the same picture on a prior use of the same drug. Blood studies were essentially within normal limits and the tourniquet test was negative. Approximately three years after the initial appearance of the purpura of antihistaminic origin, the patient again tried the same drug and similar lesions were produced in three days. A total of ten days was required for the lesions to disappear following this trial intoxication. Benadryl did not produce the lesions in ten days. Though Thephorin did not produce any purpura, the ingestion of Neohetramine did result in the appearance of a number of purpuric spots upon her lower extremities. The frequency with which purpura seems to be a manifestation of allergic reaction would suggest that perhaps this finding is not as unusual as it is thought at present. Criep and Cohen[26] have reported three instances of nonthrombocytopenic purpura as a result of penicillin sensitivity. The usual reaction of sensitivity for penicillin is noted as urticarial or edematous in type. The typical picture of serum sickness with elevated temperature,

arthralgia, edema, and urticaria was also present in the patients reported by these authors. Complete and full blood studies on these patients revealed no abnormalities in bleeding nor coagulation times. The prothrombin time and clot retraction were also well within normal limits. The purpura was thought to be upon a vascular rather than an hematopoietic basis because of a positive Rumpel-Leede test in each of the three patients. A similar occurrence of purpura following penicillin sensitivity has been reported by Spring.[123] The association of purpura and nephritis was thought to be very unusual. In contradistinction to the above report, the purpura in this instance was manifested by bleeding from the gastrointestinal tract. The patient presented symptoms in the form of abdominal pains, joint swelling, myalgia, and purpuric lesions of the skin on the day following the administration of 300,000 units of procaine penicillin. Though kidney function was definitely poor—a diagnosis of nephritis and azotemia was made upon admission laboratory studies—the azotemia eventually disappeared. The purpuric lesions were noted for a period of six weeks after the original onset of the illness. In the following six to nine months, the abnormal findings of urine examination had cleared completely, although the specific gravity did remain low. Within nine months after the discharge from the hospital, there were definite evidences of chronic nephritis. It was thought that this clinical picture was a true reaction to penicillin with the Schoenlein-Henoch syndrome being fulfilled.

Upon the use of aureomycin the patient of Gittell[58] produced evidence of collapse, weakness, syncope, and definite shock. Aureomycin had been prescribed for this thirty-six-year-old patient because of an acute exacerbation of chronic sinusitis. Nausea and diarrhea occurred within three days after the administration of the medication, when the drug was discontinued. Urticaria and angioedema were noted within a few hours after the subsequent use of a 250 mg capsule of the same drug. Hypotension, collapse, and weakness were experienced on the following morning. The administration of epinephrine and Pyribenzamine seemed to give some definite improvement. Though the symptoms of collapse were only of temporary nature, the urticaria did persist over a period of several days. In the opinion of Brown and Goodgold[16] allergic individuals who have shown marked reactions to penicillin or other antibiotics should not receive aureomycin until the skin test with serum containing aureomycin has been performed and found to be negative. The presence of an aureomycin-protein conjugate in the serum of sensitive individuals was proven by them upon skin testing their patients. Control tests were done on nonsensitive individuals. The reaction in their patients was thought to be heightened by a marked sensitivity to *Monilia albicans*. They postulate that the use of aureomycin is thought to destroy micro-organisms which previously have inhibited the growth of the Monilia in those patients susceptible to it.

Simon and Feldman[117] could find no manifestations of sensitivity to penicillin in a series of over 270 cases. These patients were treated with a penicillin-Decapryn mixture. Six of these patients had been selected from an earlier group of 175 patients that had been treated with procaine penicillin, with reactions having been noted in these six. In one patient under treatment for latent syphilis no objective signs of reaction were noted upon the use of penicillin-Decapryn, although the patient did complain of slight chill, swelling of the tongue, generalized pruritus, and pain in the chest. He had previously had a rather severe serum sickness type of reaction following 200,000 units of aqueous procaine penicillin in the past. In this same patient penicillin-Decapryn oil repository preparation was substituted for a similar mixture of aqueous base. No reaction was experienced during the six days that he received this type in over five million units. It was the opinion of these authors that the oil repository preparation of penicillin-Decapryn was far superior to the earlier aqueous mixture, about which they had reported in the year previous to this paper.

Simon[118] has repeated some of this work using a different antihistaminic agent, namely Histadyl. During the eight months covered by this survey, 1,312 patients received over ten billion units of Histadyl-penicillin preparation. Approximately half of these patients had been given penicillin in some form on previous occasions. Only six reactions from the above number of studied instances were encountered. The presence of Histadyl seemed to have a definite local anesthetic effect at the site of injection. There were no side reactions that could be determined upon a basis of the antihistaminic substance. The Histadyl-penicillin mixture was prepared so that each milliliter contained 100,000 units of penicillin and 10 mg of Histadyl or a concentration of the antihistamine recorded as 1 per cent. Berne[5] has reported an unusual type of reaction to penicillin. While under treatment with penicillin in wax for an acute pneumonia, the patient presented symptoms of reaction characterized by rash, temperature elevation, edema, and asthma. Subsequently, generalized urticaria and purpura developed, with these latter lesions eventually progressing into large subcutaneous hemorrhages. The vascular changes were most conspicuous in the veins of the ileum, the patient having developed paralytic ileus with signs of peritonitis and shock shortly before death. This author felt that the pathologic lesions of the reaction were entirely due to penicillin sensitivity. The limitation to the skin and intestinal tract was considered rather unusual in its extent. Levin and Moss[80] could find no evidence of sensitivity to penicillin in their treatment of 226 children. They used a repository type penicillin consisting of four solutions: namely, procaine-penicillin G in peanut oil with 2 per cent aluminum monostearate, and the same preparation in plain peanut oil, in sesame oil, and in aqueous suspension. These investigators carried out skin tests for both penicillin and Trichophyton on forty of these children. It was an effort to determine the possibility of the fungus infection in the skin being the sensitizing mechanism in certain patients sensitive to penicillin. They found no immediate reaction of the wheal type to either the penicillin or the Trichophyton. They are, therefore, of the impression that the low incidence of penicillin sensitivity in children as compared to adults may be due to the relative infrequency of fungus sensitivity in younger individuals. The children in this group that were definitely allergic were apparently no more liable to sensitization than were nonallergic children.

As a precautionary measure, the Board of Health of the City of New York has discontinued its program of administering prophylactic injections of whooping cough, diphtheria, and tetanus toxoids during the summer months. It was felt that there may be some association between the administration of these preparations and the local volume of paralytic poliomyelitis. The restriction on injections during the summer months was limited to whooping cough vaccine, diphtheria, and tetanus and did not include the use of pollen or other allergenic extracts.[36] It is thought that allergists are justified in carrying out any specific allergic management by injection method that may be needed by the allergic patient during the summer months. Booster stimulation with tetanus toxoid was adequate up to nine years after the primary immunization, according to the work by Bigler.[7] However, it has been recommended that the booster injections be repeated each year to assure immunity. In the majority of instances, adequate basic immunization was obtained from either two or three injections of tetanus toxoid in this study of 300 infants and children. No matter how short the interval between the last previous booster injection and an injury, the readministration of the booster dosage should be given. In this way, protective immunity is assured. The response to the booster injection was noted within the first seven days following administration. Protective levels are maintained at longer duration with a greater number of booster injections. The availability of bovine tetanus antitoxin was noted in a recent editorial.[37] The use of despeciated tetanus antitoxin had not met with success. There was evidence of severe reaction

with its use, and a good degree of caution had to be maintained in horse serum sensitive patients. Allergists alert to the dangers of prophylactic horse serum injections and the necessity of using bovine serum in those patients with naturally acquired or artificially acquired horse serum sensitivity, should welcome the return to the market of this valuable product. Fischer[52] has reported a patient in whom so-called serum neuritis was a definite and prolonged part of the picture of serum sickness. This patient was also stated to be the first case reported in which there was a marked psychotic factor. The symptoms of neuritis usually occur when serum sickness is most intense, although they may appear almost immediately after the onset or when the attack has almost disappeared. The attending physician should always be on the watch for its presence. Its occurrence is extremely uncommon. Because of the likelihood of severe serum sickness or the remote possibility of serum neuritis, it is recommended that the use of tetanus antitoxin be given prophylactically only in those patients where its need is definitely indicated. The use of this preparation for trivial reason or routine should be entirely eliminated.

In the opinion of this reviewer the use of a questionnaire as an addition to the usual complete history of allergic patients has never met with complete success. The samples submitted by Brown[13] are complete, but in the author's own admission, such a questionnaire cannot replace the actual questioning of a patient nor can it furnish the details that often must be included in such a history. Knowing the author, I am sure that he does not mean for this questionnaire to replace a thorough and accurate history, but rather that the busy physician can use this means as an adjunctive to his office procedure. Another means of completing the record has been furnished by Abramson.[1] This reviewer has always been of the opinion that there should be close association between the allergist and the rhinologist in a patient with respiratory allergy and its complications. The same opinion holds true in the patient whose allergic symptoms may be influenced by psychoneurotic tendencies or complications. This should not imply, however, that the allergist should do the work of the psychiatrist. If a patient is having complaints that are primarily upon a psychogenic basis, then that patient should be referred to a psychiatrist. Subsequently the close association between the attending psychiatrist and the attending allergist should produce the desired result. The average physician practicing allergy does not have the time nor the inclination to enter into the long psychotherapeutic recordings described by this author. It is admitted that they may be of some value to the psychotherapist. It must not be forgotten that the primary allergic symptoms are usually upon a basis of antigen-antibody relationship—a fact that is frequently overlooked when one seems to be primarily interested in the problem of psychodynamics.

There seems to be no final answer to the prophylactic use of antihistaminic drugs in instances of motion sickness. The writer in an editorial[38] felt that previous investigators had been somewhat premature in hailing Dramamine as the most effective prophylactic so far employed in motion sickness. It has been pointed out that Hyoscine had been rather markedly efficient in preventing this type of discomfort. However, Dramamine is not limited in its usefulness to the control and prevention of motion sickness alone. It has been used with good success and effectiveness in the treatment of nausea and vomiting of pregnancy. Radiation sickness may also respond to this preparation and other vestibular disturbances, such as Ménière's disease, have responded in an encouraging manner. The best conclusion to be drawn is that Dramamine will confer and has conferred a benefit on several million travelers.

After the war years, most of us thought that military regulations and rules were a thing of the past. At least we all had that hope. However, we are again faced with the problem of military regulations and paragraphs, often being called upon to interpret some of these for our allergic patients. The expense of the Government in the induction of asthmatic patients should make us all interested in this

problem. Service rendered by an asthmatic individual cannot compensate for nor justify the induction of these individuals.[39] Every allergist should familiarize himself with the standards of induction as well as with the uniform regulations that have been established for the Army, the Navy, and the Air Force. In substance, these regulations are essentially the same that were followed in World War II, although it is anticipated that the present limited mobilization will permit these regulations to be followed to the letter rather than to be modified or ignored. Hay fever in itself has never been a serious cause for rejection unless the symptoms do produce a good degree of disability. Asthma, however, is an entirely different problem. It may be relatively mild in civilian life, but the exposures of active military service may increase the severity and disability produced by the asthmatic symptoms. Each physician bears a responsibility both to the individual and to the Government in offering fair and wise advice as well as assisting application of the established standards. The Committee on Standards for Induction of Draftees into the Armed Forces (American Academy of Allergy)[24] feels that the allergic disorders of hay fever, skin diseases, and asthma may have been better classified and more inclusive. This Committee, however, stated that they were in complete accord with the provisions of the Army Regulations for Induction. Physical qualifications for the admission of members to the Armed Forces have been outlined according to a profile system, dividing human functions into six factors or divisions. In an earlier article, Halpin[63] felt that there would be no difficulty with the usual patient having uncomplicated seasonal hay fever. The admission or rejection from military service of candidates with bronchial asthma was thought to be a more serious problem and, conversely, one that would be easier to solve. The frequency of attacks and the severity of each one should have some influence upon the admission or rejection of each candidate. Consideration should be given to the type, whether seasonal or perennial asthma is present, and whether or not the asthmatic symptoms are disabling in their degree of severity. This author was much against the practice of some induction centers in admitting the applicant to the Armed Forces without thorough investigation of his asthmatic history. If adequate and correct screening of allergic individuals were accomplished during induction, a saving to the Government of no mean proportion should result. Not only is this of importance in the immediate present, but the future care and expense of these asthmatic veterans by Veterans Administration facilities is a problem that must be considered. If the allergic patient is to be accepted for military service (and in some instances, he should be), then the justification for such admission can be made only if adequate care and treatment is to be offered.

Wiseman[136] reports upon his investigation regarding the responsiveness of the flexural areas, using both specific and nonspecific urticariogenic excitants. He found that the injection of his testing solutions as close as possible to the surface of loose wrinkled skin was the most important factor in the performance of this technique. Histamine base in the dilution of 1:10,000 was used as the nonspecific excitant to produce whealing. There was a pronounced increase in reactivity of the skin of the antecubital fossa in comparison to similar technique on the arm or forearm. This was true in both atopic and nonatopic persons. In those atopic individuals tested with the atopens to which they were sensitive, there was an even greater difference in reactivity noted. The author seems to agree with previous investigators that the pH of the skin in these affected areas may have a pronounced effect upon the reactivity that is demonstrated. At least these pH findings seem to have some bearing on the localization of the atopic dermatitis, even though their mode of action has not been clarified. Lichtenstein[81] undertook a study to determine whether or not antihistamines would suppress the reactivity of bacterial antigens other than tuberculin. One hundred and forty-two tests were done on twenty-nine patients. This author concluded that the antihistaminic agents did not suppress the delayed actions

of bacterial antigens when they were injected intracutaneously. Benadryl and Pyribenzamine were the antihistaminic drugs used in this attempt to control or prevent reactions by a variety of extracts made from living bacterias.

Nineteen patients with history and clinical findings presenting definite rhythmicity were skin tested with endocrines by Meltzer.[91] He is of the opinion that endocrine skin tests are certainly not indicated in every case of acne. Those patients with a very suggestive history or those who have been observed for some time should be so tested. The use of estrogens is recommended when this endocrine aspect seems to play a great part in the production of the lesions. In addition to this rather specific form of therapy, local treatment and the regulation of dietary factors still maintain their place in the therapeutic program.

That urinary allergy is very rare is given further thought by Dees and Simmons.[31] The small percentage of true allergy of the urinary tract is considered to be due to the small amount of normal contact between foreign protein or other substances in their natural state and the mucous membrane of the urinary tract. A very good review of the literature by these investigators lends further support to the opinions expressed by them. In only 12 per cent of their group of 613 patients was any allergy determined. Because this was closely in association with the accepted 10 per cent of the general population, their conclusions were that allergy seldom was of etiologic significance in urological problems.

Extensive plasmacytosis and hyperglobulinemia due to sulfonamide sensitivity is described by Robertson.[110] He describes two cases with such findings. Autopsy findings in both instances revealed widespread plasmacytosis, hepatitis, and interstitial nephritis. Lederer[77] has stated that the tonsils should never be removed without positive evidence that this procedure is required—that the tonsil is "acutely and repeatedly" infected. He emphasizes that both the tonsils and adenoids play an important part in the development of autoimmunization in the younger child. In the allergic individual, the indiscriminate removal of the tonsils and adenoids is strongly rejected unless there is adequate evidence of disease in these tissues. Thus, localized disease might be producing rheumatic cardiac or renal complications. This investigator suggests that the nasal mucous membrane be carefully examined and that the thorough family and clinical history for allergy be recorded before a tonsillectomy is definitely considered. He is somewhat reluctant to suggest surgery in an allergic child under the age of six years. This reviewer is in complete agreement with this feeling and would further suggest that the practice of removing the tonsils and adenoids in an effort to relieve bronchial asthma in children be condemned.

Miller and Baruch[92] compared the manifestations of hostility in a group of ninety allergic children with a group of fifty-three nonallergic children. They found that the allergic child did not seem to express his hostile feelings as freely as did the nonallergic child. For this reason his symptoms may have been aggravated to some degree because of this seclusion. This sense of guilt and the resulting interconflict was based upon maternal rejection in the allergic group. Here again the expression by the reviewer regarding close association between the allergist and the psychiatrist can be emphasized. It is personally felt that the allergist should not lose sight of his problem in an effort to explain most of the allergic symptoms upon a basis of maternal rejection in infants and young children. Goodman[59] classified his twelve presented cases of neurodermatitis as mainly psychiatric in origin. The importance of a complete history, the consideration of nasal smears, and the investigation of any emotional disturbance is also stressed by Reel.[109]

In answer to a questionnaire[103] it was the consensus that any substance used for skin testing, bacterial or otherwise, would produce positive skin test reactions which were in some instances without significance. The reactions obtained in testing with Endo purified house dust extract seemed to indicate that in proper dilutions there

was a definite relationship between the positive reaction and the patient's clinical problem. Because of this knowledge of "false positive" and "false negative" reactions, many allergists and other physicians have come to the belief that skin testing with foods is of little or no value. That this discrepancy may be due to the failure by the physician to employ the antigens in an active form for skin testing is the basis for an editorial.[40] Evidence has been offered that the use of fresh or quick frozen material will produce more significant reactions than will prepared extracts from commercial sources. It has been presumed that fruits, berries, and shell fish may contain antigens which are readily destroyed by enzymatic action. Their same properties are preserved by quick freezing. Some antigens may be destroyed by cooking, but even though this does not occur, they may be lost in the preparation of an extract.

Because of the resemblance between the electroencephalograms of allergic children and those of patients with convulsive disorders, Dees and Lowenbach[32] have considered the possibility of allergic epilepsy. They have studied thirty-seven children under the age of fourteen years from the standpoint of allergy and electroencephalography. Their present study was not primarily designed to test the value of any therapy but rather to survey the clinical findings to determine whether or not the allergic factors could be of any clinical importance. Antiallergic management in these thirty-seven children suggested that improvement of the allergy was related to improvement in the convulsive disorders. The concept of allergic epilepsy was considered to be worthwhile if the recognition of allergy as a contributing factor would be the means of removing even a few patients from the group of idiopathic epilepsy.

The importance of severe reactions from insect stings should be brought to the attention of everyone in the practice of allergy today. Swinny[125] feels that the severity of the reaction is dependent upon antigenicity of the foreign substances, the quantity of the substances, and the degree of sensitivity of the subject. Marked emphysema, overdistention of the right side of the heart, and hepatic engorgement are three typical findings of post mortem examination in deaths by insect anaphylaxis. Slower reactions are characterized by coughing, itching, urticaria, uneasiness, pallor, cyanosis, and dyspnea. On occasion the reaction may be abdominal in character with cramps, vomiting, and defecation followed by loss of consciousness. In extreme emergencies epinephrine intracutaneously or intravenously is the only drug to be considered. The importance of insect allergy in our daily living has also been emphasized by Bowen.[10] Variation in degree of reaction is dependent upon the degree of sensitivity possessed by the patient as well as the specificity of the insect. Sensitization is difficult to induce in a nonsensitive person. Hyposensitization in the sensitive person is even more difficult and equally as transient. This author feels that papular urticaria should be considered to be upon a basis of insect bite reaction. Hyposensitization for mosquito, bee, wasp, and yellow jacket sensitivity is thoroughly recommended. Emergency measures should be employed where indicated. These consist chiefly of the use of epinephrine 1:1000 fortified by antihistaminic measures. Spider bites are treated with calcium gluconate and magnesium sulfate. The best remedy for the care of a sensitive patient is the preventive measures that are very thoroughly described by this author.

The importance of aspirin as a sensitizing agent has been emphasized by several authors during the past few months. Though the accepted theory is that most aspirin sensitive patients are skin test negative, Walton and Bottomley[134] were able to obtain positive reactions to direct tests with aspirin in 50 to 75 per cent of their subjects. They observed aspirin sensitivity in twenty-two of 830 successive hospital admissions even though only 13 per cent of the entire group were considered to be advanced cases of asthma. They advocate the need for caution in the administration of all medications to asthmatic patients, with a particular reference to aspirin. In

opposition to the above skin test finding with aspirin, Mathews, Lovell, and Sheldon[90] were unable to produce larger reactions using aspirin-containing sera than when testing normal sera. Twelve patients were used in this study. Negative results were likewise obtained in passive transfer studies where previously prepared sites were tested with aspirin-containing sera, control sera, and saline solutions of aspirin. Because of their negative findings on skin testing, these authors consider that the only reliable method of diagnosing aspirin sensitivity at the present time is found in the words of a complete and thorough history. No degree of dependency can be placed upon the reaction by skin test. Feinberg and Malkiel[46] are in agreement with the above authors regarding skin test reactions in the aspirin sensitive individual. These latter writers feel that there is no satisfactory method at present for determining aspirin hypersensitivity in a patient. The oral ingestion, though reliable in producing a prompt response, is considered to be too dangerous for practical application. Direct skin testing and passive transfer techniques have been consistently negative. Their opinions were based upon investigative procedures using guinea pigs which were sensitized to aspirin by the use of aspirin-protein conjugates.

Since heparin is usually obtained from beef liver or lung, it would seem quite likely that a fairly large number of cases of sensitivity would be encountered in clinical practice. Gotz[60] has reported a fifty-nine-year-old male patient whose long-standing asthma (the patient was comparatively free at the time of the introduction of the medication) was markedly aggravated by the administration of heparin sodium. Within thirty minutes after the use of this preparation, his asthmatic symptoms were of extreme variety and were associated with and complicated by the appearance of giant urticaria. He points out that the majority of reported cases of heparin sensitivity have been due to gradual sensitization. Gotz' patient, however, had never received heparin at any time prior to the initial administration which resulted in this provoked attack.

It is necessary that we must learn far more about what appears to be familiar before the problem of food allergy can be effectively tackled. The divergent views upon the subject of food allergy are adequately described and discussed in an editorial[41] stating that much remains to be done before the subject can be adequately explained. There has been much discussion regarding the possibility of allergic reactions in corn sensitive patients resulting from the intravenous injections of dextrose. Feinberg, Huber, Black, and Figley[48] have written in answer to an editorial concerning such reactions. They disagree with the given impression of the frequency with which corn sensitivity is found in the practice of allergy. Other investigators had claimed that approximately twelve out of one hundred of the general population have allergic symptoms from the ingestion of refined corn products. These correspondents do not agree, in view of the millions of intravenous injections of dextrose which have not resulted in the numerous allergic reactions or fatalities that could be expected were the foregoing true in its entirety. At the same time, Loveless[83] could not find a single instance of sensitivity for corn sugar, syrup, or oil by history or deliberate feedings. Only a very few persons were located by questionnaire who developed reproduceable symptoms from corn starch in large quantities when it was fed in the "blindfold" manner. Ratner[108] was in complete agreement with the above correspondence. As a result of animal experimentation in his laboratory, his conclusion was that corn syrup is nonanaphylactogenic. The basis for this opinion was the complete hydrolysis resulting from heating corn starch in the presence of pure hydrochloric acid. He has stated that the soluble proteins of corn starch become insoluble in the process of cooking. In a poll of allergists conducted by Loveless[84] clinical symptoms from ingested corn were encountered in only 0.16 per cent of their 45,000 patients. She makes an appeal for the introduction of controlled, objective methods in the study of food allergy. This is particularly important in view of the high incidence of corn sensitivity reported by

other investigators. Corn starch does not contain enough antigen to affect most corn sensitive patients when eaten in the usual quantities. This conclusion by Cazort[18] was based upon "blindfold feedings" of corn starch, arrowroot, and tapioca puddings to patients supposedly sensitive to corn antigen. Randolph and Yeager[106] have emphasized the high incidence of corn sensitivity and have suggested that some of the refined corn derivatives are also allergenic offenders. Using the same technique as these authors, Bernton[6] could find only one fifth as many instances of corn sensitivity. He strongly questions the validity of the above mentioned syndrome of food allergy. The minor symptoms enumerated by some authors as a result of food sensitivity are open to question and should not be considered as diagnostic of an allergic reaction to the ingestion of food.

Leibowitz and his co-workers[78] believe that the question of food allergy is one not dependent merely on the method of testing. The interpretation of results parallels the quality of the testing material. They could determine no relationship between the frequency of positive skin test reactions and the positive clinical trial with the individual food being ingested. Fish and nuts yield the highest number of negative skin tests, with the highest number of positive clinical ingestion trials being noted in these same foods. The expected clinical importance of wheat, milk, and egg was not confirmed by this study. They were able to confirm clinically the significance of 35 per cent of all positive food skin tests. The reliability of the negative skin tests was emphasized by the low incidence of positive clinical trials with foods that were negative on intradermal testing. These investigators were of the impression that inhalants, pollens, and bacteria were far more important than food allergy in the respiratory cases that were investigated. The importance of ophthalmic testing with food allergens has been described by Shulman.[114] The eye test showed itself superior both in detecting an allergic condition and in its reliability to show a positive or negative test. A positive reaction was recorded with a marked injection of the sclera about twenty minutes after the installation of the test allergen. The diagnosis of food sensitivity can be based upon the production of definite symptoms by the ingestion of a food when no other cause can be demonstrated. With this as a working premise, Davison[30] emphasizes the importance of food sensitivity in the production of nasal allergy. As a result of his study in 368 patients, food sensitivity could be demonstrated of marked importance at any age. Food sensitivity must be considered in any patient with nasal allergy who has had adequate treatment but still has a persistence of symptoms. An investigation of a patient's food sensitivity is advised by this author in all patients with nasal allergy, whether seasonal or perennial in its characteristics.

Gastrointestinal allergy has been seen clinically to follow the ingestion of foods, drugs, and beverages. The symptoms of gastrointestinal allergy may also be associated with the oral administration of serums, drugs, pollen extracts, or the inhalation of certain vapors. Thomas[128] has noted the symptoms of gastrointestinal allergy to mimic any other pathology of this system. This subject is of primary importance in children complaining of abdominal pain occurring in combination with other symptoms and with all degrees of nausea and vomiting. The importance of excluding nonallergic pathology before a definite diagnosis of gastrointestinal allergy is made has been emphasized by this author. He has cited various case reports which demonstrate the various types of gastrointestinal involvement. Muecke[95] also considers gastrointestinal allergy as a cause of intestinal manifestations. He cites instances in which the vomiting usually due to hypertrophic stenosis of the pylorus has not been relieved until the offending food has been removed from the infant's diet. The removal of the offending food is suggested as the best form of therapy for this condition. Desensitization for food sensitivity may be attempted. Failures in such instance are usually attributed to a lack of patience. Diarrhea, constipation, flatulence, abdominal pain, and even intestinal hemorrhage may be due to gastrointestinal

allergy. Atwater[4] considers the allergic factor in gastrointestinal disease when other methods of approach become ineffectual. The importance of minor symptoms and signs in food allergy may be emphasized by proper investigation. Arp[3] found that minor symptoms were most evident in those who had been under treatment for chronic asthma or some other major allergic condition. The relief of the major allergic complaints permitted a persistence of minor symptoms such as pruritus, eczema, urticaria, recurring "colds," nasal obstruction, canker sores, headaches, colic, or flatulence. The role of food allergy in the causation or aggravation of organic disease of the intestinal tract has suffered because of the lack of objective methods of study. Lepore and his co-workers[79] have used X-ray examination of the small intestine as an objective method in the study of gastrointestinal allergy. They describe specific cases, with interesting X-ray findings, in whom the diagnosis of food allergy was often entertained only after the motility of the small intestine had been reported as abnormal. The patient of Blumstein and Johnson[9] remained symptom-free from his gastrointestinal complaints on a sea-food-free diet. This asthmatic patient had not had any known food, drug, nor inhalant sensitivity. Because of physical examination and laboratory findings, a diagnosis of acute appendicitis was made and surgery was performed. The pathologist's report revealed that the entire wall of the removed ileum—the surgical appearance of the lesion seemed to be that of terminal ileitis—was infiltrated by myriads of eosinophilic leukocytes. These authors do not contend that allergy should be considered of any importance in the etiology of regional enteritis even though their patient has fulfilled the clinical, pathologic, and etiological requirements for such a diagnosis. Further importance of allergy as a part in the production of acute abdominal complaints has been discussed by Sneierson and Mazar.[119] It is their impression that a tendency towards hemorrhage and diapedesis should call the physician's attention to the possibility of allergy. During an acute attack of asthma, remarkable changes were noted in the gastric mucosa by gastroscopy. Lichstein and Benjamin[82] report a marked change in the stomach folds with increased redness, mucus, and edema. This was sufficiently marked to prevent continued gastroscopy. A return to essentially normal gastric appearance was noted after the administration of epinephrine 1:1000.

Criep and Riley[27] have reported an instance of agar sensitivity which emphasizes the importance of this substance as an occupational offender. Direct and indirect skin testing corroborated by sniff tests confirmed a clinical impression that the patient was definitely sensitive to this material. The authors reviewed the frequent use of this product in our present-day living. The employment of agar in the dairy, confectionery, and bakery business is emphasized, the material frequently being used in sherbet, icing, and meringue. Dental impression compounds and liquid petrolatum emulsions as prepared in a pharmacy are also containers of agar. This patient was adequately treated with an extract of agar which permitted him to return and continue his work as a baker.

The frequency with which milk allergy is recognized in infants has been emphasized by Clein.[21] Fourteen different and unrelated groups of symptoms were analzyed by this author. The most frequent symptom as a result of milk sensitivity was eczema. These skin lesions were present in 42 per cent of the 140 patients studied. Vomiting as a result of milk sensitivity comprised a large group. These babies continued to have symptoms until "they either outgrew their milk allergy" or a substitute formula was arranged. This reviewer feels that the statement as quoted above is used all too often and can be misleading. It is my opinion that these infants never outgrow their allergic complaints though the clinical picture may change to some degree as the patient advances in years. Colic, diarrhea, emotional upsets, head and chest colds, asthma, constipation, urticaria, and others were listed by this author as due to clinical milk sensitivity. Complete relief was obtained in all

these patients by the avoidance of cow's milk and substitution of a soy preparation. Most of these infants were able to tolerate milk after abstaining for three to four months, although 15 per cent were unable to tolerate milk after the age of one year. Clein advocates a milk-free routine for all individuals suspected of having a milk sensitivity. Growth and development were not disturbed in infants fed soya-bean milk during the first three months of life. Sternberg and Greenblatt[124] determined serum protein values on fifty-five newborns. Normal protein values were noted in these infants under study when the sole source of proteins for the first three months of their life was soya-bean milk. They state that the use of this milk substitute is indicated without any fear of detrimental effects being caused by the diminished intake of animal proteins.

In the treatment of a patient with food sensitivity, it is important for the physician to make a diagnosis of cause. It is equally important for the patient to receive adequate instructions regarding the substitution of foods to his diet so that his nutrition will be adequate and complete in all respects. This poses quite a problem in some instances when a patient is sensitive to many of the grains. Some foods seem to possess a low index of sensitivity. Rada[104] has stated that poi is a carbohydrate food of high nutritional quality that still possesses a low degree of allergenicity. Poi is used as a staple food for healthy infants and children in the Hawaiian Islands. It is also recommended for individuals with specific health problems. In that area it is a staple member of the average diet. This food is nutritious and is highly digestible, with a good mineral and vitamin content. The mineral content of poi compares favorably with that of white potatoes and rice, with the calcium content being about the same of white potatoes. The phosphorus content is somewhat lower than that of rice, potatoes, and most cereals. Poi also contains an excess of basic elements in the ash which may be important in building and maintaining sound teeth. This Hawaiian food is a poor source of vitamin A and contains less ascorbic acid and thiamin than do cooked white potatoes. Its use in soft diets and as a substitute for grain in the elimination routine has been recommended. At the present time there has not been sufficient demand from the physicians of the mainland of the United States to warrant the marketing of this product. However, it is my impression that if the practicing allergist were to realize the availability of such a food product, the demand could well be met. It was my opportunity to use poi as a cereal or grain substitute during military service in the Hawaiian Islands. It proved to be very satisfactory for the purpose for which it was employed at that time. In the past year samples of this material have been obtained and have been used with very good results in those patients sensitive to grain and other cereals. It is a very satisfactory addition to the diet for an infant, regardless of the age of the patient. If any of the readers of this review are interested in trying poi as a grain or cereal substitute, I would be very glad to arrange for a supply to be made available to them.

One of the most complete and revealing discussions of gastrointestinal allergy is that submitted by Kohn.[75] This author feels that there is a definite correlation between food dislikes and food allergy. Though the allergic reaction is not often recognized by the patient, the avoidance of certain foods by that individual is often due to an association of disagreeable symptoms upon the ingestion of that food. Highly sensitive individuals may react to even minute amounts of the offending foods, or the tolerance may differ in individuals and in the same individual under different conditions. Kohn feels that the incidence of gastrointestinal allergy is much greater than is appreciated. The mechanism of the allergic reaction in the gastrointestinal tract is the typical antigen-antibody reaction that occurs in any sensitized tissue. The essential pathology too is the same that occurs in other areas, namely, smooth muscle spasm and edema. The occurrence of gastrointestinal symptoms should always arouse suspicion of food or drug allergy, particularly in those

patients with associated asthma, eczema, or other allergic conditions. A careful history, physicial examinations, various laboratory tests, and therapeutic or clinical trial food elimination should be completed before a diagnosis of organic pathology is accepted without confirmation. He suggests that routine food testing be done because a positive reaction to a food by this method of testing is significant. Actual feeding tests are of definite value. Elimination or provocative diets are considered to be of important assistance. Kohn feels that a sensitivity to a single food is a rarity, although in some instances the multiplicity of foods may tend to increase the difficulty of proper management. The avoidance of a food for a period of time will often allow for tolerance when such foods are ingested subsequently at intervals. He states that the use of a rotating diet is of extreme importance in the avoidance of the development of food allergy as well as in the proper management of the patient with a food allergy.

Zindler[139] obtained favorable responses in 125 patients with food allergy when Pyromen was used in therapy. Best results were obtained in those patients in whom a specific diagnosis was made and the allergy had been partially controlled before Pyromen therapy was instituted. This author had no explanation for the failure of some patients to respond favorably to Pyromen therapy. He thought, however, that some failures might be overcome by dosage adjustment or by a correct interval between the administration of the drug. In Zindler's opinion, the use of Pyromen was more effective in the treatment of food allergy than in the inhalant types.

Relief of migraine with Dramamine has been reported by Brenton.[12] The more severe the distress, the more beneficial seemed to be the reaction. In none of the seven cases reported by this author had relief been obtained by any previous treatment. Recent simplification of the management of the acute migraine attack has been described by Fuchs and Blumenthal.[57] The simplification has resulted from the demonstration of the synergistic effect of caffeine with ergotamine tartrate. Effective self-administration of these preparations by mouth or by rectum in the acute migraine attack has also been a feature in the simplification. Their patients were instructed to use suppositories of Cafergot. Fifty-eight of sixty-nine migraine patients noticed excellent results. The vast majority of their patients responded very well to a 2 mg dose representing that amount contained in one rectal suppository. Thirty-five of their patients experienced nausea and vomiting following medication, but twenty-eight of these experienced these symptoms in their untreated attacks. The same preparation used in the treatment for relief of tension headaches has proved disappointing. The authors also present criteria for the differentiation between migraine and tension headaches. A definite relationship between emotional upsets and the occurrence of headaches in fifteen children was the result of a study by Katz and his co-workers.[69] Some member of the family in eleven of these fifteen children had had severe headaches of one sort or another. In six of these eleven the diagnosis of migraine had been made. Gross evidence of neurosis could be determined in nine children. Ogden[98] states that the failure of oral Cafergot may often be explained by the delay in the administration of the medication. It should be used as early as possible in order to obtain the best possible results. The blood level of the drug determines its pharmacologic effect within the individual, with variations from one individual to the next. The preparation must be used in sufficient quantity to obtain the pharmacologic response. One tablet three times daily is not likely to prevent nor relieve a headache. Two tablets of the medication can be given at the onset of symptoms. If there is no relief after half an hour, then another tablet should be taken, with a repetition of this every half hour up to six tablets or until relief is obtained. The use of the ergotamine drugs will relieve an impressive percentage of cases of frontal headache. Some of these frontal headaches may be associated with respiratory allergy, the correction of this latter condition eventually affording the relief of the headache.

It is a common finding to observe allergic children who have had tonsillo-adenoidectomies with little apparent relief from their respiratory complaints. Price and Solow[100] were struck with the greater number of such operations performed on their studied patients. Usual incidence of this operation among pediatric patients admitted to the medical service was noted to be 13 per cent. In children with positive skin tests, however, the incidence of tonsillectomy and adenoidectomy was found to be 48 per cent. Roentgenographic evidence of sino-bronchial disease was demonstrated in 64 per cent of allergic children under the age of five years. It was quite evident that a pattern of ready susceptiblity to lower respiratory tract infection was established in those patients presenting a familial factor of allergy together with positive skin test reactions. A predominant eosinophilia proved to be quite accurate in 84 per cent of twenty-six pediatric patients. Because diagnostic standards for bacterial allergy are not universally accepted, Chobot and his associates[20] have employed a modified criteria for the diagnosis of bacterial hypersensitivity. These features include a personal and family history of allergy, repeated respiratory infections associated with asthma, eosinophilia, leukocytosis, and the ability to produce an attack of asthma with a given dosage of autogenous vaccine. Their study included 400 children whose asthma had begun before the age of three years. Only one child of the 400 studied had asthma resulting from a food sensitivity among other causative factors. Inhalant sensitivity was the etiology of 10 per cent of the cases, and infection was proven in 30 per cent of these patients. A single cause for the asthmatic complaints was noted in 41 per cent, but multiple causes of the asthma were found in 59 per cent. One of the most important causes of the bronchial asthma in this group of patients was chronic focal infection. Bacterial allergy may simulate any allergic syndrome. They are of the impression that the incidence of food allergy in childhood asthma has been grossly overestimated. This opinion was based upon their clinical findings. Feingold[49] felt that bacterial antigen were productive of irreversible or fixed tissue changes. This was in contrast to the edema, the spasm of smooth muscle, and the stimulation of glands that is induced by inhalant or ingested antigens producing reversible tissue changes. He is of the impression that bacterial infection may produce tissue hypersensitivity with irreversible tissue changes characterized by death of cells and vascular damage. Thus, infection may influence the course of existing allergic disease caused by sensitivity to antigens. He feels that infection is primarily one of influence rather than one of cause. Of paramount importance is the control of the inhalant or ingestion type of allergy. He condemns the use of either stock or autogenous vaccines, particularly in children.

The allergic background manifests itself as allergic tracheitis or as a pre-asthmatic sign. This type of cough may signal the end of a true bronchial spasm or it may initiate a similar affair. Brown[14] adequately explains the main characteristics of differentiation between allergic cough and the symptoms of tuberculosis. The tuberculous cough will vary as to the site of the lesion. In the acute stage of the disease, it may at first resemble the cough of pneumonia or an acute bronchitis. Tuberculosis should be considered in a diagnosis of any chronic cough of any type. The cough in bronchiogenic carcinoma will depend upon the type of growth, with the remaining symptoms depending upon the location of the neoplasm.

The pathologic findings in extrinsic and intrinsic types of asthma were found to be the same by Walton, Penner and Wilt.[135] The older patients showed more emphysema, but otherwise age did not modify the pathological findings. Nine patients in their series of individuals who came to the autopsy table had had heavy sedation of Demerol, morphine, or intravenous anesthetics prior to the fatal termination. McDermott and Papper[87] have also reported three instances of pronounced respiratory depression following intravenous use of Demerol. Actual precipitation of asthmatic

symptoms during anesthesia was produced in three other patients by the intravenous administration of this drug.

McLeod[89] reviewed the symptoms and signs of allergic rhinitis. She found that lymphoid tissue was increased in both allergic and infectious conditions, with nasal polyps being the usual result. Presence of infection seemed to perpetuate the allergic manifestations in that treatment of the former without any specific therapy did seem to lessen the allergic involvement. The regression of nasal polyps is more likely to occur when the allergic background or the sinusitis is brought under control. Van Alyea[133] advises the removal of nasal polyps when breathing is impaired or sinus drainage is obstructed. Strenuous surgical procedures upon the sinuses seldom affords more than temporary relief in asthmatic patients. An appreciation of the importance of allergy in rhinosinusitis is productive of better over-all results. In this same symposium Brown[15] adequately discusses nasal function and nasal neurosis. He decries the continued use of nose drops, inhalors, and other mechanical means of relief in the patient with a nasal allergy. In this instance he feels that the only desirable treatment lies in the re-education of the patient and the ultimate correction of the basic allergy. Treatment directed against the chief complaint in the patient with nasal symptoms must also take into consideration functional disturbances.

In a study of inhalants, Alternaria occurred most frequently in a survey determined by the plate method under the direction of Prince.[102] House dust was the most widely distributed allergen of the miscellaneous inhalant group. This author advises the mold sensitive patient to follow precautions against house dust. These mold sensitive patients should always be instructed to escape grain harvesting or grain handling operations. Since the soil is the universal habitat for molds, most of the common forms in the atmosphere are thus widely distributed. Zivitz,[140] on the other hand, was rarely able to find Alternaria on exposed plates in the Miami, Florida, area. He was of the impression that his high incidence of positive skin test reactions to Alternaria was due to previous exposure. The apparent sensitivity was developed by these patients during their residencies in the North. Penicillium, Aspergillus, Helminthosporium and Hormodendrum were found to be more seasonally of greater signficance in this area than were the other members of this group. The highest mold counts by the plate method in the Miami area were noted during the winter season from November to May.

Kuhn[76] has recommended the use of lavage in cases of chronic eosinophilic otitis. He has suggested that the physician remember the sensitizing effect of certain medications, particularly sulfathiazol powder. The accompanying allergic background should be uncovered. If such is an impossibility, the use of autovaccine has had a beneficial effect in the hands of this gentleman. It is his impression that the chronic infections with eosinophilic characteristics are much easier to treat and are much less likely to become complicated than are the eosinophilic type. These latter are more chronic in their reactions.

An instance of unusual reaction to pollen sensitivity has been described in a case report by Mulligan.[96] His patient was an eight-year-old child with marked pruritus vulvae which occurred only during the ragweed season. Oral antihistamines gave the best relief of any measures that had been attempted. Desensitization with ragweed extract subsequently gave complete relief. For the first time in several years, she was entirely free of symptoms during the pollen season. Mulligan has suggested the name "vaginal pollenosis."

The importance of castor bean sensitivity has been presented by Figley and Rawling.[51] They have reported nine cases of sensitivity to this allergen. They recommend that dericinized castor bean extract be included as a part of each allergist's routine list of testing materials. So potent is this factor that testing by any method other than by scratch or dermal is to be condemned. In addition to the above authors,

Coulson, Spies and Stevens[25] have also established unequivocal evidence of castor bean allergen as a contaminant of green coffee.

In every case of chronic, obscure pulmonary disease, a diagnosis of actinomycosis should be considered. Pittman and Kane[99] have reported the importance of early diagnosis in these cases. The prompt use of sulfonamides, penicillin, or streptomycin is very effective in eradicating the infection. The clinical picture must be consistent with the isolation of the organism, as a diagnosis of actinomycosis should not be made upon his latter finding alone. *Candida albicans* is the one member of this genus that is commonly associated with human disease. Oblath and his associates[97] have presented a very interesting and complete review of the subject of pulmonary moniliasis. Their case reports are illustrative of various features of this unfortunate condition. Whether pulmonary moniliasis is a primary disease entity or not is a controversial question. A diagnosis of this condition can be made only from the proper examination and carefully collected sputum specimens, with study being made for *Candida albicans*. The first case of bronchial asthma due to *Candida albicans* to be reported in medical literature was the presentation of Keeney.[70] His patient had had an oral infection due to this fungus for about three months preceding the onset of his respiratory symptoms. The infection in the bronchi persisted for about six months before the manifestation of bronchial asthma became clinically apparent. Large immediate skin reactions were obtained with the concentrated fungus broth filtrate. These reactions could be successfully passively transferred. Effective treatment of this condition was completed by the use of a 10 per cent solution of sodium caprylate in propylene glycol. A stronger solution seemed to prove irritating to the bronchial mucous membranes.

The uses of bacitracin, aureomycin, chloromycetin, and terramycin in dermatologic diseases have been outlined by Miller and his associates.[93] Bacitracin is effective against Gram-positive organisms and quite ineffective against Gram-negative organisms. Its greatest application is in the field of local therapy. Its topical application is an entirely safe procedure, with its index of sensitivity being very low. In the past, aureomycin has had minimal reports on acquired sensitivity, but in recent months evidence of such ability on the part of the drug is beginning to appear. Chloromycetin possesses an advantage over aureomycin in that there is an almost complete lack of side-effects with its use. These authors have reported that they have neither seen nor heard of instances of skin sensitization with the use of this preparation. There is a very low incidence of side-reaction in using terramycin. For local application, it has been shown that oil-in-water and greaseless bases release the various antibiotics much more effectively than bases such as petrolatum. Mitchell[94] is of the opinion that dermatitis due to streptomycin never develops except upon direct skin contact. Withdrawal from contact has led to prompt recovery in his cases. Because of this feature, the condition is preventable under properly controlled conditions. The appearance of a very extensive rash and vesiculation was noticed on the ninth day of streptomycin therapy by the patient of Harris and Walley.[65] Though the medication was discontinued, the dermatitis progressed through stages of vesiculation to complete exfoliation. There was gradual, spontaneous clearing over a period of successive weeks. Hypersensitivity to streptomycin is much more common in people who handle the drug than in those who receive it. Cohen and Glinsky[22] have determined that such hypersensitivity develops only after prolonged and intimate contact with the drug. They consider exfoliated dermatitis to be a rare but serious complication of streptomycin contact. The importance of both patch testing and intradermal testing has been stressed by these authors. Positive tests are usually delayed, and no immediate reactions were noted. The earliest positive intradermal test done by these men showed local edema in six hours. The earliest positive patch test was noticed with severe itching after eight hours' application.

The skin is one of the best and the most practical indicators of the immune and

allergic state. Kierland[71] has expressed the opinion that the skin is useful in the diagnosis of various diseases ranging from tuberculosis and asthma to small pox and diphtheria. Skin complaints may be a source of local or systemic disease. This is best demonstrated by generalized itching, which is a very common symptom referable to the skin. The appearance of purpura should suggest a very careful, general study. This author urges the physician to take advantage of the important help offered by the skin in the diagnosis of underlying disease.

Contact with a recently lacquered bar in an officer's club in Japan produced an outbreak of dermatitis venenata. Etter[44] found the lesions to be typical of poison ivy dermatitis localized to the forearms, hands, and face. A violent skin reaction was noted with scrapings of the lacquered wood on patch testing a known poison ivy sensitive member of the detachment. Controlled tests with scrapings of unlacquered wood were negative. Urushi lacquer is obtained from urushiol, the active principle of a Rhus plant very similar to that producing poison ivy. The active principle of both these plants was found to be hydroxyl urushiol. The author calls attention to the use of this lacquer in various art and souvenir objects, all of which should be classified as potential sensitizers to the poison ivy patient. Individual susceptiblity and individual reaction are two features which make the evaluation of therapy in Rhus dermatitis a difficult problem. Hoagland, Myers and Cosand[67] also considered other variables to be the extent and duration of exposure to the plants as well as secondary trauma and the duration of dermatitis. These authors used a variety of medication in treating ninety-two patients with 217 areas of Rhus dermatitis. They are of the impression that the speed of recovery from this type of inflammation is not dramatically influenced by any agent applied to the surface of the skin. Acceleration of recovery seems to be aided by warm compresses or by locally applied antihistaminic preparations. They have recommended the employment of creams or solutions containing local anesthetics. If the lesions are oozing or have the appearance of cellulitis, the application of warm, moist compresses is to the patient's advantage. The appearance of kidney disease due to a sensitivity of Rhus toxin has been reported by Shaffer and his co-writers.[112] They have reported two patients in whom the kidney complications were thought to be sensitization phenomena. This possibility was suggested by the latent period between the last injection of the Rhus toxin and the first sign of kidney disease. The renal involvement was an acute, rapidly advancing process with marked fulminating clinical signs. One of their patients was a fatality. Because of the eosinophilia, urticaria, and histologic changes in the kidney, death was thought to be of an allergic nature. Because of the great potential danger associated with the administration of this preparation, Rhus extracts should not be used in the active treatment of plant dermatitis.

The thoroughness with which exclusion of egg from the diet and environment of a sensitive patient must be completed has been emphasized by Cazort.[19] This food should be removed from the home and from the family diet for at least three weeks before the statement of complete elimination can be fulfilled. Cazort's patient failed to show any improvement until such an extreme measure was accomplished. In patients with infantile eczema, markedly sensitive to egg, this author feels that similar responses can be expected as normal.

Because of the likelihood of sensitization in the average patient with infantile eczema, topical application of sulfonamides, penicillin, and streptomycin is contraindicated. Rostenberg and Riddell[111] feel that aureomycin may be an exception to the above rule. They warn against vaccination for small pox in the presence of severe eczema except under emergency conditions. Though Roentgen ray therapy may be of some temporary benefit, these authors are of the opinion that this is radical treatment and is somewhat ill-advised. Of the variety of conditions grouped under the label of infantile eczema, the atopic and seborrheic varieties are most commonly seen in practice. Distinction between these two types cannot be made except by time

alone. The importance of egg, wheat, potato, and milk as positive offenders in infantile eczema has been noted by Epstein and Palacek.[43] They emphasize that a skin test reaction to a certain food, however, does not necessarily mean that the eczema is connected with this food or even that the child is allergic to that allergen. It is true that the patient may be highly allergic to a nonreacting food test. They state that the positive reaction to egg-white in infantile eczema often may indicate a sensitivity that has been acquired prenatally, with the antigen being transmitted through the placenta. In contrast to this, the sensitivity to wheat usually is acquired by the infant after birth.

The first step in the therapy of contact dermatitis is a correct diagnosis and the determination of the causative factor. Downing[34] states that the inflammatory reaction may consist of erythema, edema, papulation, vesiculation, oozing or crusting, or any combination of these lesions. Antihistaminic ointments are of some value in certain selected cases. In the presence of erythema, edema, and vesiculation, therapy usually should consist of hot and cold wet dressings, followed by a soothing lotion and a bland paste. Treatment should be continuous. He emphasizes the danger of injecting the antigenic *Rhus toxicodendron*. Physicians are exposed to many irritating chemicals and infections in their professional routines. For this reason, the presence of occupational dermatoses in physicians is rather common. Epstein[42] has found that contact dermatitis is the commonest type of injury suffered. Infections are comparatively uncommon but may be acquired accidentally from patients by the physician. Penicillin has been demonstrated to be five times as frequent a cause of dermatitis in physicians as has streptomycin or dihydrostreptomycin. The importance of radiodermatitis is stressed by this author. Though there is no excuse for this occupational dermatitis in the present day, instances are still encountered. All in all, however, the appearance of dermatoses among physicians today is less common than one would expect in consideration of the hazards to which the average physician is exposed. Tobias[129] has outlined six rules for diagnosing a cosmetic eruption. Important is the appearance of the eruption within twenty-four hours after the use of the new cosmetic. With the exception of nail polish dermatitis, the skin lesions should first appear at the site of the application of the cosmetic. Most of the lesions will have morphology that is seen clinically in contact dermatitis. Improvement in the lesions should appear within a week after discontinuing the suspected cosmetic. A recurrence of the eruption in the same location should follow a reapplication of the suspected cosmetic. The importance of the patch test has also been emphasized. This author is of the opinion that the dermatitis caused by sensitivity to cosmetics is not as common as might be expected considering their widespread use. Most of the dermatitis today has been produced by new products which often contain skin sensitizers. Cosmetics were found to be the most frequent cause of periobital dermatitis by Swinny.[126] Cream-based shampoos, nail dyes, and liquid polishes were also considered to be of marked importance in the production of these symptoms. It was this author's finding that atopy played little or no direct part in the study of this condition. When patients were found to be reactive to one cream-based shampoo, they were usually reactive to most other brands of this same product. Overtreatment was responsible for periorbital dermatitis in twenty of sixty-three patients.

A learned discussion of altered permeability of membranes has been presented by Harrell and Aikawa.[61] This altered permeability may result within a few minutes to a few hours with the Meningococcus. Pneumococcus pneumonia produced such a change within a few hours to a few days, whereas trichinosis will alter the membrane permeability within a period of a few days to weeks. In the absence of infection, such alterations may occur during immune reactions as noted in serum sickness, resembling very closely the changes seen during acute infectious diseases. Cell membranes themselves are probably not altered whether the cells are

directly parasitized or not. Alterations in the permeability of membranes are qualitatively similar, whether produced by bacterial infection or by immune reaction in the absence of infection. The thorough work of Blatt[8] makes one agree with the author that rheumatic fever and infectious arthritis are diseases caused by bacterial allergy. In the presence of certain but not all bacterial filtrates, the blood leukocytes become necrotic in less than eighteen hours. This is true in patients exhibiting the clinical manifestations of these diseases. Though injections of filtrates to which a patient is not sensitive produce no reaction, overdosage during the desensitization program does reproduce the syndromes of the diseases. Grove[61] has found foods to be unimportant as a cause of vasomotor rhinitis. The chronic form of this condition is more common than the acute, and is caused very frequently by hyperplastic sinusitis and inhalants. Ninety-eight of 105 patients with vasomotor rhinitis due to infection eventually came to surgery. The greatest majority of operations were performed upon the sinuses. Poor results obtained by surgical measures can often be explained by incomplete surgery. Twenty per cent of Grove's operated patients were completely relieved and 77 per cent were definitely improved. Sixty-nine per cent of 200 asthmatic patients experienced complete or definite relief from their asthma following surgery. This author does not overlook the need, however, of treating the etiologic sensitizations that may be encountered.

The coming years should be productive of additional interesting and learned presentations by these and other contributors.

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AMERICAN COLLEGE OF CHEST PHYSICIANS

The Fifth Annual Postgraduate Course in Diseases of the Chest sponsored by the Council on Postgraduate Medical Education and the Pennsylvania Chapter of the American College of Chest Physicians and the Laennec Society of Philadelphia, will be presented at the Warwick Hotel, Philadelphia, Pennsylvania, March 24-28, 1952.

A program covering the entire field of heart and lung disease is being arranged. Dr. Chevalier L. Jackson, Philadelphia, President of the American College of Chest Physicians, is chairman of the postgraduate course committee.

Physicians interested in attending the postgraduate course are invited to communicate with the Executive Offices, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

College Decennial Anniversary

The American College of Allergists was incorporated as a nonprofit organization in November, 1942. It may be fitting at this time to quote excerpts from the first editorial which appeared in the initial issue of the ANNALS:

"The American College of Allergists came into existence because of the deep-seated conviction of its founders that a liberal organization, based upon and combining the principles of humility and justice, is needed to fill an important gap in the present structure of allergic affairs. In all sincerity, the College invites the cooperation, respect, and support of all those who consider allergy as a specialty, and who share the conviction of its founders that the internist of the future must be, first of all, a master of allergy. . . . . Recognizing and upholding reasonable standards, the policy of The American College of Allergists is to be, at all times, a liberal and democratic one, a fact which should prove especially heartening to the younger men interested in this specialty, who need the encouragement that comes with early and fitting recognition."

At the time of the founding of the College, total membership in allergy societies in the United States amounted to approximately 200 physicians. Today, ten years later, there are three national allergy societies with a membership of 1500. One year after the College was organized, the two older societies known as "Eastern" and "Western," then twenty years old, each having been founded in 1923, united to form The American Academy of Allergy. In the past ten years national societies have been established in many countries throughout the world, and within three years after the College was launched the International Association of Allergists was incorporated. The first international congress of the latter was held in Zurich, Switzerland, in September, 1951, attended by 600 people from twenty-eight different countries. Allergy as a specialty has had an unprecedented growth during the past decade.

The College was organized with a membership of forty-five. Today its membership has grown to 1,050. Its roster contains the names of many outstanding allergists noted for their accomplishments in both investigative and clinical fields of allergy and allied subjects. Many hold positions of great importance in institutions of higher learning, while others are to be found on the staffs of accredited hospitals.

The College was the first allergy society to elect as associates immunologists, biochemists, plant pathologists, botanists, et cetera, and to receive their valuable consultation, services, and advice.

Although ANNALS OF ALLERGY is the official College publication, the *Quarterly Review of Allergy and Applied Immunology* is also published under its auspices. The ANNALS was the first allergy journal to publish practical clinical papers as well as articles on investigative allergy and also the first to have departments for editorials, questions and answers, news items, and comprehensive reviews of the literature. Under the heading "Progress in Allergy" its readers receive a most valuable and unique service. The first issue of the ANNALS averaged eighty-nine pages, exclusive of

advertising, and eight pages of advertisements. During the past year the issues contained 140 pages and thirty-one pages of advertising. The mailing list of the ANNALS is now 2500. Four books have been published by the College:

1948 H. A. Abramson: *Psychodynamics and the Allergic Patient*
1949 French K. Hansel: *Allergy in Relation to Otolaryngology*
1951 Bret Ratner: *Allergy in Relation to Pediatrics*
1952 Stephan Epstein: *Allergic Pruritus. Its Dermatologic Management.*

At its first annual meeting in Chicago in 1944, the College initiated intensive graduate instructional courses, and these courses have been continued annually ever since.

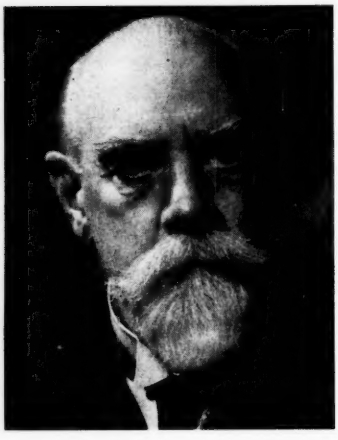
Most of the accredited medical schools in the United States, as well as the Veterans Bureau Hospitals, have departments of allergy. From the outset, the College has maintained that allergy should be recognized by the Council on Medical Education and Hospitals of the American Medical Association as a clearly defined medical specialty possessing an autonomous board. Since allergy now embraces about fifteen disease entities, and since some of the most important come under specialties entirely apart from internal medicine and pediatrics, allergy should be considered a specialty which must be correlated with *every* other specialty of medicine. The Academy and the College have a joint certification committee on allergy which has appeared annually for the past five years before the Committee on Standards and Education requesting an independent board and rejecting subcertification by the American Boards of Internal Medicine and Pediatrics. As evidence of the complete failure of subcertification in allergy, at this writing only forty-three physicians certified in pediatrics and 137 certified in internal medicine have been subcertified in allergy out of 1500 physicians who are Fellows of the American Medical Association. Many of these men who are certified in their respective specialties are today conscientiously devoting all or the greater part of their professional time to the treatment of allergic ills, because these ills now rank third among serious diseases. This discrimination against the allergist and his recognition projects a problem which can be solved only by the combined efforts of the three national allergy societies.

We must continue to raise our educational standards in allergy so as to command the respect of all impartial physicians. Regardless of the unfair attitude of a minority in refusing to recognize allergy as a separate specialty, College membership continues to grow rapidly, and the excellent qualifications of the majority of applicants for membership is most noteworthy.

While one could go on enumerating the achievements of the College since its inception, perhaps a few words of tribute are in order to those responsible for its development. Remarkable indeed has been the *esprit de corps* of its founders and officers. All have worked unselfishly, and impartially and at much sacrifice of time, effort, and money in the constant carrying on of its original principles and the furthering of its aims and purposes. As one peruses volume after volume of the ANNALS down through the years, the identity of those primarily responsible for the growth and success of the College is clearly revealed. As the official publication of the College, it will also serve in the years to come as an historical monument to their illustrious achievements.

In Memoriam

PROF. DR. ROBERT DOERR



It was with sorrow that the officers of the College received a notice from the bereaved family of the death of Prof. Dr. Robert Doerr of Basel, Switzerland, January 6, 1952. Prof. Doerr was elected an Honorary Fellow of the College on June 26, 1946, at its annual meeting in San Francisco. This was also the occasion of the First Pan-American Congress on Allergy. Prof. Doerr presented a paper on "The Integration and Differentiation of Allergic Phenomena," which subsequently appeared in the ANNALS for September-October, 1946.

Prof. Doerr was born at Tecsö, Hungary, November 1, 1871. At seven years of age he lost his father, an Austrian railroad engineer. Through the support of his uncle he obtained his high school training at Brünn and later his studies at the Medical Faculty of the University of Vienna. Although he wanted to study biology, he considered it to be a profession without prospects. In 1897 he was graduated as a doctor of medicine and then served for some time as an army doctor. Fortunately, during his military career he was able to work at the Institute of Pathological Anatomy in Vienna, and he published various scientific papers under the guidance of Prof. Baltauf, for whom he had the deepest admiration.

In 1908 he obtained the "venia legendi" for general and experimental pathology at the University of Vienna, and soon afterwards he was appointed to the professorship. In 1919 he accepted the chair of Hygiene and Bacteriology at the University of Basel. From 1919 to 1943 he was uninterruptedly engaged in research work, infectious diseases, immunology, and allergy being his special interests. He once said that a life was valuable when it had been long and full of work; he fulfilled this motto, since even at the age of seventy-eight he undertook (and completed just before he died) a work on allergy. Allergy was the field which always held the greatest fascination for him.

He published in his lifetime 230 well-prepared and authoritative articles, bacteriological and pathological reports on various infectious diseases, dysentery, filtrable viruses, and so on. His major publications were on anaphylaxis and immunology, and throughout the world the literature on these subjects quotes Prof. Doerr's concepts and observations. His article on allergic phenomena in the *Handbook of Physiology,* 13th edition, is a milestone on the basic mechanism of allergy. His publications were extremely wide in scope. Some of his associates were men like Berger, Hallauer, Zdansky, Jadassohn, and Seidenberg. Through the years he was presented with many prizes and honorary memberships.

Like all truly great scientists, he was extremely modest, almost reticent, but firm in his convictions. It was the writer's good fortune to have Prof. Doerr as a guest in his home and enjoy the intimacy of his charming personality. The officers and members of the College extend their sincerest sympathy to his survivors, Bertha Maria, Agathe, Edith, and Rico.

News Items

NEWS ABOUT ACA MEMBERS

Adrian H. Scolten, M.D., F.A.C.A., of Portland, Maine, spoke in Washington at the Second National Hoover Reorganization Conference on behalf of the nation's doctors. Speaking with Doctor Scolten were former President Hoover, Senator Paul Douglas, Senator William Benton, and Senator George D. Aiken. The Hoover Report found the federal medical system "a confused, wasteful, and competitive aggregation of some thirty-five agencies, all striving to outdo each other in obtaining Government funds and competing for scarce personnel and facilities, while performing conflicting tasks." Doctor Scolten charged that efficiency and economy were given insufficient thought in locating, building, and staffing hospitals, estimating that the cost of this wasteful system runs about two billion dollars annually. He recommended that both House and Senate act on bills which have been before them for a year to unify and streamline the federal medical system in accordance with the bipartisan Hoover Commission recommendations.

Doctor Scolten, who was educated at Washington University Medical School, St. Louis, has been active on the political scene. He was a candidate for Congress in 1948 and 1950, and he has been recommended for Ambassador to Holland and for the United Nations Delegation.

CUBAN SOCIETY OF ALLERGY

At elections held December, 1951, the following Fellows of Sociedad Cubana de Alergia have been elected to the Executive Committee:

President:	Dr. Julio de los Santos
Vice President:	Dr. José Pedrera
Secretary:	Dr. Fermín Alpizar
Treasurer:	Dr. J. Amiguet
Members:	Drs. G. Estrada de la Riva, José Cadrecha, and José M. Quintero Fossas.

DRUG ALLERGY

Dr. Umberto Serafini, who will collaborate with Prof. Di Mattei for the clinical section on the subject of drug allergy during the next Fifty-third Italian Congress of Internal Medicine, requests that readers of ANNALS OF ALLERGY send him reprints or references from their works on drug allergy. Those who have material are urged to send it to Prof. Umberto Serafini, Largo della Gancia, 5, Rome, Italy.

ALLERGIST SEEKING PRACTICE

A young Associate Fellow of the College is interested in either purchasing a practice or in associating with another allergist or a group. He is thirty-two years old and has had five years of clinical training in allergy. He would prefer a location in the eastern part of the United States. Those interested may write to ANNALS OF ALLERGY, 401 LaSalle Medical Building, Minneapolis 2, Minnesota, for further information.

BOOK REVIEWS

THE MERCK INDEX OF CHEMICALS AND DRUGS. Sixth Edition. 1167 pages, thumb indexed. Price $7.50. Rahway, N. J.: Merck & Co., Inc., 1952.

This work contains 8,000 descriptions of individual substances, more than 2,000 structural formulas, and about 20,000 names of chemicals and drugs alphabetically arranged and cross-indexed. It is a desk encyclopedia for those engaged in chemistry, pharmacy, medicine, dentistry, and allied professions. The Index, along with The Merck Manual of Diagnosis and Therapy and The Merck Report, has served the medical profession for more than half a century. The Index has become internationally recognized as a most reliable source of information in the various fields mentioned.

New features of this edition include a table of standard buffers for calibrating pH measurements; a table of radioactive isotopes, giving their half lives and type of radiation; and a table of current medical uses for radioactive elements and compounds. A new section lists more than 300 organic "name" reactions with original and review references, together with a description and structural representation of each reaction. There are an up-to-date periodic table, a table of international atomic weights, and appendices on such subjects as coal-tar colors for foods, drugs, and cosmetics; thermometric equivalents; antifreeze mixtures; refractive index of liquids; saturated solutions; percentage solution tables for apothecaries; and atomic weights and their multiples and logs.

The new features, together with those time tested, make the volume one of the most complete references of its kind in existence. It is a handy, compact book bound in attractive dark blue Fabrikoid.

TEXTBOOK OF MEDICINE. Eighth Edition. Edited by Russell M. Cecil, M.D., Professor of Clinical Medicine Emeritus, Cornell University; Robert F. Loeb, M.D., Professor of Medicine, Columbia University; Alexander B. Gutman, M.D., Professor of Medicine, Columbia University; Walsh McDermott, M.D., Associate Professor of Medicine, Cornell University; Harold G. Wolff, M.D., Associate Professor of Medicine, Cornell University. 1627 pages, 204 figures, 40 tables. Price $12.00. Philadelphia: W. B. Saunders, 1951.

The new eighth edition of a textbook which has been a standard for students and practitioners of medicine for over twenty-four years encompasses in a single volume an authoritative discussion of those diseases which comprise internal medicine. In this edition the authors stress the physiologic, biochemical and psychologic aspects of disease and consider them in the discussion of specific diseases throughout the book. There are twenty articles which have not appeared in previous editions, some of the subjects being Q fever, the collagen diseases, carbon tetrachloride poisoning, beryllium poisoning, chronic amphetamine poisoning, vitamin B_{12} deficiency, amyloidosis, pulmonary function in health and diseases, and bone tumors. Yet through careful selection the editors have been able to shorten the book by 136 pages without the omission of any important material.

The section on diseases of allergy is written by a somewhat circumscribed group of authors with a limited viewpoint and in some instances represents controversial personal opinions. The term "intrinsic asthma" is used freely and only serves to confuse; it describes a condition which even the coiner of the term cannot define. It implies only that the patient may not have had a sufficient diagnosis. Atopic eczema, an extremely common form of allergic dermatitis in children and adults,

is not discussed, whereas much less frequent and relatively unimportant allergic diseases are presented. Special mention should be made of Doctor Cooke's chapters on the history of allergy and on hay fever. One subject which could have been easily added as a timely chapter is industrial diseases in relation to internal medicine.

The binding is handsome, and the illustrations are excellent.

THE 1951 YEAR BOOK OF MEDICINE. Edited by Paul B. Beeson, M.D., Professor of Medicine, Emory University Medical School; J. Burns Amberson, M.D., Professor of Medicine, Columbia University; William B. Castle, M.D., Professor of Medicine, Harvard University; Tinsley R. Harrison, M.D., Professor of Medicine, Medical College of Alabama; George B. Eusterman, M.D., Mayo Clinic. 696 pages, 149 illustrations. Price $5.00. Chicago: Year Book Publishers, 1951.

This year book is a comprehensive and balanced review of practical value. It brings to focus the hundreds of important new developments published in the voluminous literature on medicine in the past year. The editors, all outstanding authorities, have succeeded in editing 523 articles, both foreign and domestic.

In the section on infections a new epidemic respiratory disease is described; and there are discussions of antibiotic combinations, vitamin therapy, ultraviolet light in control of acute respiratory infections in schools, and factors affecting epidemics of poliomyelitis. The chapter on the chest is up to date, including discussions of BCG inoculations, pneumoperitoneum treatment of pulmonary emphysema, streptomycin-PAS therapy in tuberculosis, lipoid pneumonia, and data on smoking and cancer of the lung. The chapter on the blood presents new therapy for pernicious anemia, leukemia and Hodgkins' disease. The final chapters cover such topics as salt-free diet for hypertension, a new method of the diagnosis of gallstones, the use of Banthine, and benign gastric polyps. This one of a series of fourteen year books contains reliable editorial comments from outstanding authorities in their field and presents the latest developments which are most helpful in the daily practice of the general practitioner or the specialist.

ANTIBIOTIC THERAPY. By Henry Welch, Ph.D., Director, and Charles N. Lewis, M.D., Medical Officer, both of the Food and Drug Administration. 562 pages. Price $10.00. Washington: Arundel Press, 1951.

This is a clinical desk guide for the use of the antibiotics in the infectious diseases. There are twenty chapters, nine dealing with the isolation and the development of the antibiotics and eleven covering their effect on the infectious diseases. The antibacterial activity, pharmacology, dosage, and clinical use are presented in precise and orderly detail. It is a guide to the whole field of antibiotic therapy. Particular attention is given to doses and vehicle of administration. Contraindications, complications, and side reactions are discussed. Microbiology and biochemistry are presented as an adjunct to the clinical use of the antibiotics. The incidence and nature of allergic reactions are tabulated and explained. Thirty-six effective graphical summaries give the information in ready-to-use form.

THE NEUROSES. Diagnosis and Management of Functional Disorders and Minor Psychoses. By Walter C. Alvarez, M.D., Mayo Clinic. 667 pages. Price $10.00. Philadelphia: W. B. Saunders, 1951.

Any book written by this well known authority always proves most interesting and unique. This volume represents the experience in diagnosis and treatment achieved by forty-five years at the largest clinic in the world. The author presents in a relaxed style many patients with puzzling neuroses and functional troubles.

Doctor Alvarez, being an internist and not a psychiatrist or neurologist, looks at neuroses from the point of view of the physician confronted every day with diagnostic problems, not from the restricted viewpoint of the psychiatrist. He describes neuroses as they are encountered by the specialists at the Mayo Clinic. Thoughtful physicians now are realizing that it is necessary for them to be better informed on the minor psychoses and functional troubles.

Chapters are included on the handling of nervous persons, on the art of convincing them that their trouble is a neurosis, and on the art of teaching them that they can help themselves.

To enjoy fully the contents of this excellent book, the physician should read it from cover to cover instead of merely consulting a chapter in time of need.

BIOLOGICAL ANTAGONISM. The Theory of Biological Relativity. By Gustav J. Martin, ScD., Research Director, The National Drug Company, Philadelphia. 516 pages, 64 figures, 44 tables. Price $8.50. Philadelphia: The Blakiston Company, 1951.

This volume presents a thorough yet concise study of the author's theory of biological relativity—that "general law" which underlies all biological activity and is fundamental to the resolution of all problems in biology. It is a new science, bringing within its scope elements of biochemistry, pharmacology, chemotherapy, immunology. Biological antagonism is based upon biological relativity, the latter concept involving the idea that there is no single molecular structure which itself alone possesses a function not shared by another molecule, even though closely related. Living units follow a pattern based upon relativity, and their constancy of composition and form is based upon antagonism. With this concept the author takes an entirely new view of biologic worlds. It forms the basis for evolution, every other phase of biology, even the underlying principle of life itself.

Twenty-two chapters deal with biological antagonism as reflected in natural and synthetic displacing agents, amino acids, purines, pyrimidines, vitamins, hormones, and minerals. Biochemists, pharmacologists, immunologists, and others interested in the fundamental study of this interesting subject will find this unusual review thorough and clear, since in one volume it crystallizes the whole theory of biological relativity.

The binding, paper stock, and printing come up to the usual excellent Blakiston standard.

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